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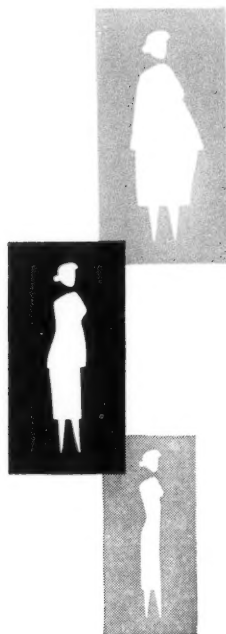
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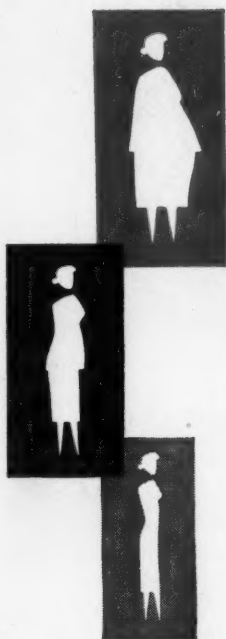
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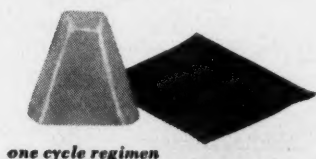
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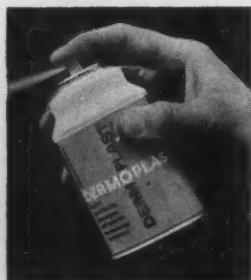
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1 TRICHOMONAS VAGINALIS INFECTION

prevalence of the disease

The protozoan flagellate *Trichomonas vaginalis* "...is now recognized as occurring in association with leukorrhea of vaginal origin more frequently than any one other specific organism..."¹ In approximately 25 to 35 per cent of women with symptoms of vaginitis, *T. vaginalis* is at fault.

Although vaginal trichomoniasis may be found in children and in women past the menopause, its greatest incidence is during the period of sexual maturity. It is somewhat more common in the nonpregnant state than during pregnancy, when candidiasis (moniliasis) occurs more frequently.

Approximately 58 per cent of males whose wives have trichomoniasis harbor the organism.² In a recent report, Coutts³ notes that among 2,482 males with nongonococcal urethritis, *T. vaginalis* was found in 1,690 (68 per cent).

presenting complaints in women

"Leukorrhea is the most constant and the most characteristic symptom of vaginal trichomoniasis. Almost invariably, this is associated with some degree of irritation or itching of the genital structures, and, frequently, there may be other local complaints such as dysuria, dyspareunia, or irritation of the neighboring skin areas, particularly the inner aspects of the thighs."¹ Postmenstrual exacerbation of symptoms, particularly increased discharge and itching of the vulva, is common.¹

clinical findings

vulva and neighboring structures—In the typical acute case, the labia are edematous and inflamed. There may be acute dermatitis of the perivulvar skin and the inner aspects of the thighs. The urethral orifice may be prominent or pouting and frequently contains the same discharge present in the vagina and on the vulva. Because of the general inflammatory reaction, associated involvement of Bartholin's or Skene's glands is difficult to detect.

vagina and cervix—The vaginal mucous membrane may be deeply congested and deep red or vermillion in color, instead of the normal pale pink. In some cases, the vaginal papillae are prominent and granular, so that the vagina assumes a "strawberry" appearance. The cervix itself is not involved. The external os and cervical canal are usually normal. However, in protracted and recurrent infection, endocervicitis and cervical erosion may develop.

discharge—Characteristically, the vaginal discharge has a pathognomonic "frothy" appearance. It is usually profuse, purulent, of a fluid consistency and often foul. Its color varies from creamy white to yellow-green to grayish yellow. In the presence of severe inflammation, the discharge may even be blood-tinged.

Fig. 1.

Clinical appearance of the vulva showing "frothy" discharge characteristic of trichomoniasis.



pathologic findings in the female

Trichomonas vaginalis is found in the exudate adjacent to the vaginal mucosa, in Bartholin's and Skene's glands and in other areas, along with leukocytes and a variety of secondary invaders. In trichomoniasis, the customary chief inhabitants of the healthy vagina, the Doderlein bacilli, either disappear completely or remain in markedly reduced numbers. The normal vaginal acidity (pH 4.0 to 4.8) decreases somewhat, so that the pH ranges from 5.0 to 6.0, with an average value of 5.5.

Fig. 2.
Hiding places of *Trichomonas vaginalis* in the female:

- A. Vagina
- B. Urethra
- C. Bartholin's gland
- D. Skene's gland
- E. Endocervix
- F. Bladder



infection in the male

In contrast to *T. vaginalis* infestation in the female, similar infestation in the male is often asymptomatic. For this reason, it has frequently been overlooked in the past. Infected husbands, even though asymptomatic, are a source of reinfection. The trichomonads may be present in the preputial sac, urethra, prostate, seminal vesicles, epididymis, bladder and, more rarely, the upper urinary tract.

Fig. 3.
Hiding places of *Trichomonas vaginalis* in the male:

- A. Preputial sac
- B. Urethra
- C. Epididymis
- D. Prostate
- E. Seminal vesicles
- F. Bladder



2

DIAGNOSIS OF TRICHOMONAS VAGINITIS

clinical examination

The appearance of the vulva, the vagina and, particularly, the discharge is often so typical that the experienced observer can make the diagnosis of *Trichomonas vaginitis* by clinical inspection. However, not all cases of vaginal trichomoniasis present the customary appearance. Consequently, before starting treatment, it is advisable to verify the diagnosis by microscopic demonstration of the organism.

decisive diagnosis

wet smear—Although not as accurate as the culture method, the easiest, quickest and most convenient method of demonstrating trichomonads is by the wet smear. This requires only an ordinary glass slide.

For making a wet smear, a cotton-tipped applicator containing secretion from the posterior fornix is placed in 1 or 2 cc. of physiologic saline, Ringer's solution or *Trichomonas* Diluent, Ortho, rotated, removed and rolled on a glass slide. The smear thus made is then examined under low magnification. *Trichomonas* Diluent, Ortho, facilitates demonstration of trichomonads because with this diluent, trichomonads appear colorless and *motile*, while cellular components of the vaginal smear are pink and nonmotile. *T. vaginalis* is the only flagellated protozoan in the human vagina.

Under low magnification, trichomonads are readily detected as clear, actively motile, pear-shaped organisms, slightly larger than pus cells. Their body shape changes readily, and their movement is characteristically darting or jerky.

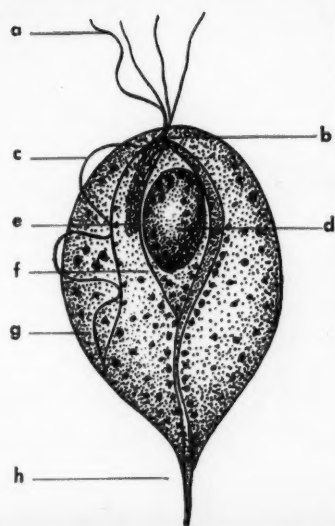


Fig. 4. Structure of *Trichomonas vaginalis*:

- A. Four anterior flagella
- B. Blepharoplast
- C. Undulating membrane
- D. Nucleus
- E. Parabasal body
- F. Parabasal fibril
- G. Posterior flagellum
- H. Axostyle

At the anterior end of *T. vaginalis* are four flagella which move with great rapidity. Along the side of the protozoan, starting from the base of the flagella and ending about midway along the body, is an undulating membrane which also beats rapidly. Extending from the posterior portion is a stiff appendage, the axostyle. Under continued observation, trichomonads can be seen to degenerate gradually. They become rounded ("pseudocyst"), disintegrate and ultimately disappear completely. There is no true cyst formation. Reproduction is by binary fission.

culture—Demonstration of trichomonads by culture is unnecessary in clinical practice. It is essential, however, in research projects and clinical investigations concerned with the efficacy of trichomonacidal agents. Only by negative culture can a distinction be made between *true cure* and *apparent cure* (symptomatic relief).

The recent work of Kean and Day⁴ has substantiated the reliability of the culture method for detection of trichomonads. In 80 women with vaginal trichomoniasis, culture with Simplified Trypticase Serum (STS) medium was positive in 100 per cent. The hanging drop was positive in 76 per cent, and the stained smear in 74 per cent. In not a single instance was a patient positive by hanging drop or stained smear, and negative by culture.

3

NEED FOR SYSTEMIC THERAPY

cure versus temporary relief

Until the advent of systemic therapy with TRITHEON tablets, eradication of *T. vaginalis* had been difficult to obtain. Transitory symptomatic relief had been the usual result with all methods of topical treatment.

recurrences

There is a remarkable tendency to recurrence of Trichomonas vaginitis after apparent "cure." As noted by Trussell: "Failure to cure vaginal trichomoniasis is suggestive of resistant forms but also suggests that (1) rectal, urethral and glandular involvement were overlooked, (2) treatment has been inadequate or inappropriate, (3) reinfection has occurred, or that (4) a drug-resistant strain has developed."⁵ *In the light of recent research, it appears that recurrences are due mainly to the inability of local therapy to eradicate the trichomonads from inaccessible places in the female urinary and genital tracts, and to reinfection from husbands.*

In view of the problems involved in trichomoniasis, it is evident that local therapy must often fail. Only systemic therapy, reaching all the hiding places of the trichomonads in both the female and the male, can possibly be expected to succeed in effecting a *true cure*.

criteria of cure

Symptomatic relief, though often readily obtainable, is not evidence of cure. From the practical clinical standpoint, negative smears indicate probable cure. In clinical investigations, however, conclusive evidence of cure of trichomoniasis can be established only by means of negative cultures. In all evaluations of TRITHEON tablets in males and females, proof of cure was established by culture methods using Simplified Trypticase Serum (STS) medium.⁶

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4 CLINICAL EFFICACY AND SAFETY OF TRITHEON TABLETS

eradication of trichomonads

Clinical investigation has conclusively demonstrated that TRITHEON tablets administered orally eradicate trichomonads for culture-proved cure of more than 70 per cent of female patients whose husbands are treated simultaneously with TRITHEON tablets.⁷

case studies

In Perl, Guttmacher and Raggazoni's² series of 174 women whose husbands were **not** treated, 35 per cent were cured clinically and parasitologically. This was determined by *negative cultures* with STS medium done two weeks after cessation of therapy and repeated two to four weeks later. Similar results were obtained by Plentl,⁸ who treated 78 patients, 30 of whom were pregnant.

In a series² of 48 males, the diagnosis of trichomonas infestation was established in 28, by culture of the seminal ejaculate. Of the 28 males treated with TRITHEON tablets, 16 were cured after one course of systemic treatment and two after a second course. The remaining 10 failed to bring in a post-treatment semen specimen.

safety of TRITHEON tablets

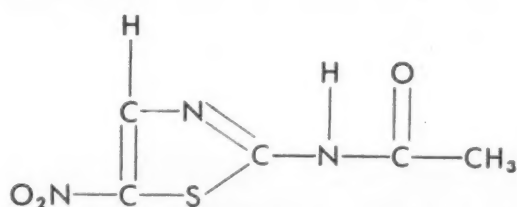
TRITHEON tablets are well tolerated.^{2,8} There has been practically no gastric intolerance, and side effects have been absent or negligible. No effect on the hemogram has been observed. In some patients the urine may be colored brown. This is due to a metabolite of aminitrozole and is not related to blood.⁹

5

ACTIVITY AND PHARMACOLOGY OF AMINITROZOLE

chemical structure

TRITHEON tablets are composed of 2-acetylamino-5-nitrothiazole (aminitro-
zole). They contain no arsenic, bismuth, silver, mercury, iodine or antibiotics
and are completely different from other trichomonacides both in chemical
structure and oral efficacy.



2-acetylamino-5-nitrothiazole (aminitroazole)

trichomonacidal activity in vitro

When compared with commonly used topical agents, the trichomonacidal
effect of TRITHEON tablets is from 75 to 1,500 times as great.

comparative trichomonacidal efficacy

| Agent | Maximum Killing Dilutions (In Vitro) |
|-------------------------------|--------------------------------------|
| Aminitroazole (TRITHEON) | 1:1,500,000 |
| Phenylmercuric acetate | 1:20,000 |
| Silver picrate | 1:18,000 |
| 5,7 diiodo-8-hydroxyquinoline | 1:1,000 |
| Bismuth glycolyl arsanilate | 1:1,000 |

trichomonacidal activity in vivo

In vivo studies⁹ utilizing the mouse peritoneum have also demonstrated the outstanding action of aminitrozole against trichomonal infection. White mice were inoculated intraperitoneally with pure cultures of *Trichomonas foetus* grown in STS medium. *T. foetus* was used rather than *T. vaginalis* because it is more pathogenic for the mouse. Aminitrozole was administered in varying doses, starting on the day of infection or on the fifth day after infection. Of the control animals, 95 per cent developed intraperitoneal infection and 55 per cent died. In the animals receiving aminitrozole, the morbidity and mortality rates varied from 0 to 10 per cent. The effectiveness was greater when the drug was administered early. The authors concluded that aminitrozole "...in dosages of 50 and 100 mg./kg. was highly or completely effective in eradicating the experimental body cavity infection of *T. foetus* in mice."⁹

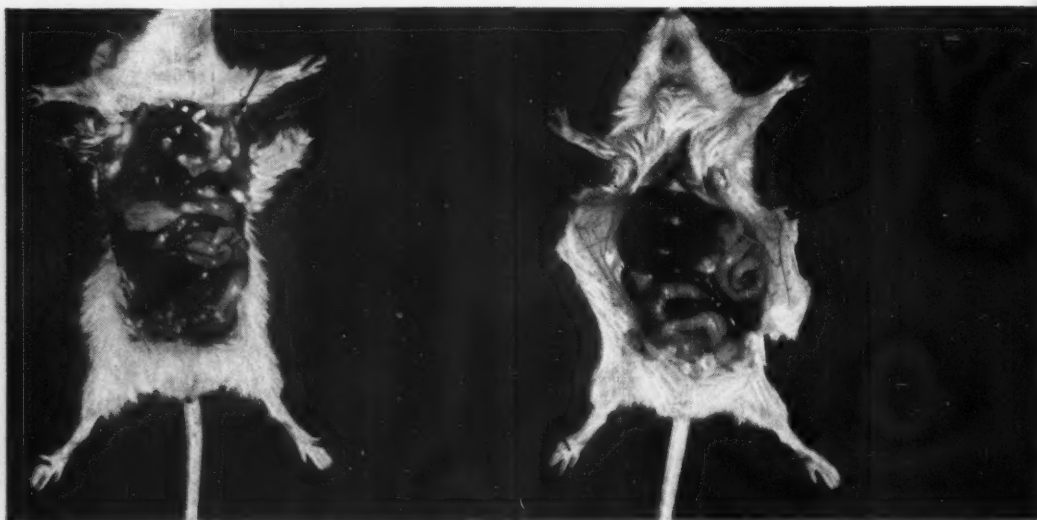


Fig. 5. Trichomonacidal action of aminitrozole:

A. Control: peritonitis following intraperitoneal infection with *Trichomonas foetus*.

B. Treated with 2-acetyl-amino-5-nitrothiazole: no peritonitis in similarly infected mouse.

results of toxicity studies

Exhaustive acute, subacute and chronic toxicity tests have established the safety of aminitrozole.⁹ It is characterized by a low oral and intraperitoneal acute toxicity in several species (rat, mouse, chicken, turkey and dog). Subacute and chronic toxicity studies in the dog and monkey showed no evidence of impaired liver or kidney function, no change in the chemical constituents of the blood and no leukopenic effect.

6

TREATMENT WITH TRITHEON TABLETS

treatment in the female

Dosage is one tablet (100 mg.) orally, three times daily, for ten days. To speed relief of vaginal irritation and inflammation, adjunctive soothing local therapy may be prescribed. Aci-Jel® therapeutic vaginal jelly is particularly suitable because of its blandness and physiologic pH. In resistant cases, the course of treatment with TRITHEON tablets may be repeated.

treatment in the male

It is most important that the husband be treated at the same time as the wife. Dosage for the male is the same as for the female. To avoid reinfection, patients should refrain from marital relations during treatment.

TRITHEON TABLETS

brand of aminitrozole

indications:

TRITHEON tablets provide effective oral therapy for trichomoniasis in the male and female.

composition:

Each tablet contains 100 mg. of
2-acetyl-amino-5-nitrothiazole (aminitrozole).

recommended dosage:

One tablet orally, three times daily, for ten days. In resistant cases, a second course of treatment may be prescribed.

available:

Bottles of 30 and 180 tablets.

adjunctive therapy in the female:

To speed relief of vaginal irritation and inflammation, local therapy with Aci-Jel therapeutic vaginal jelly is recommended.



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1. Anz, U.E., and Smith, L.J.: Clinical Evaluation of Chlorpromazine in the Management of Labor, Am. J. Obst. & Gynec., in press.

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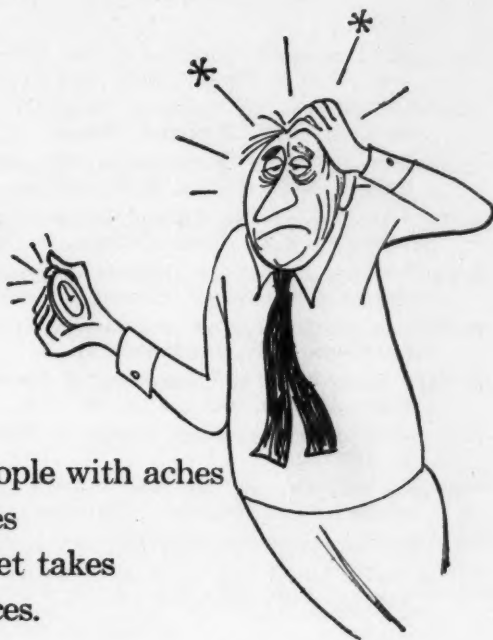
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American Journal of Obstetrics and Gynecology

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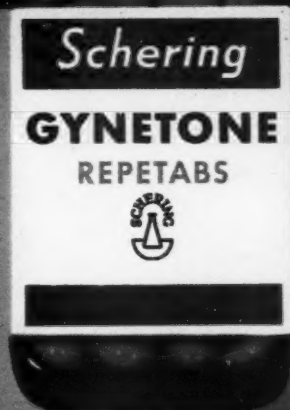
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1. Moyer, J. H., in discussion of Galen, W. P., and Duke, J. E.: Out-patient Treatment of Hypertension with Hexamethonium and Hydralazine, South. M. J. 47:858 (Sept.) 1954.

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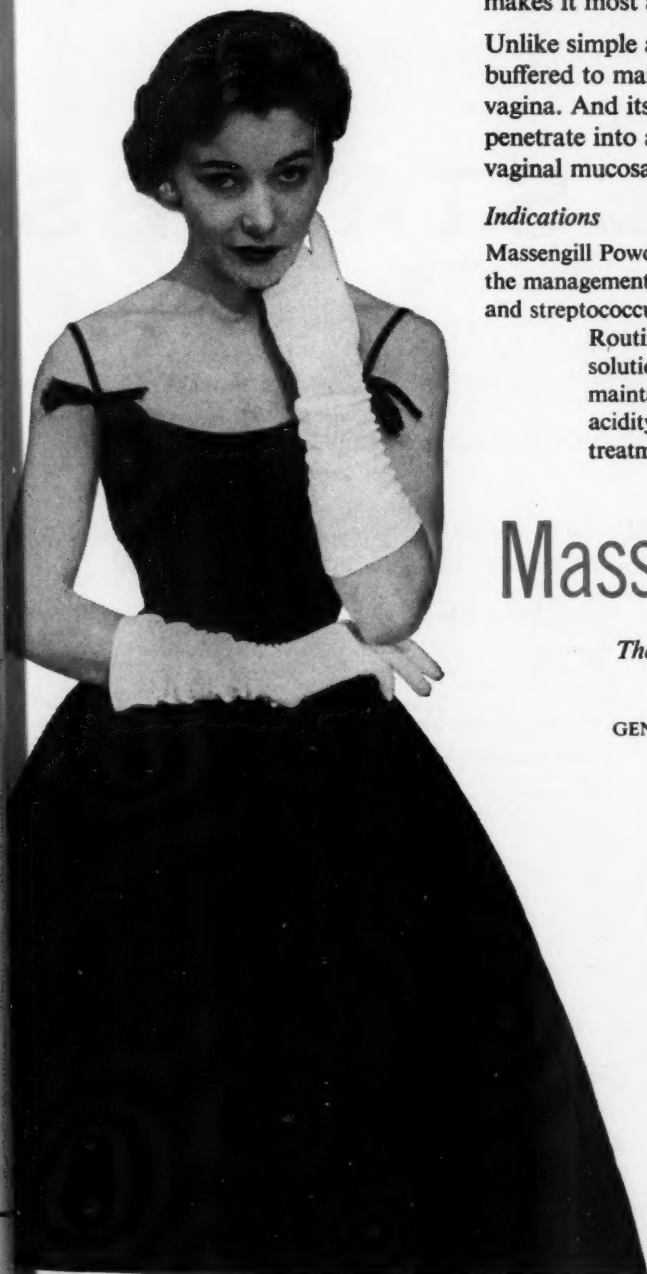
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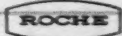
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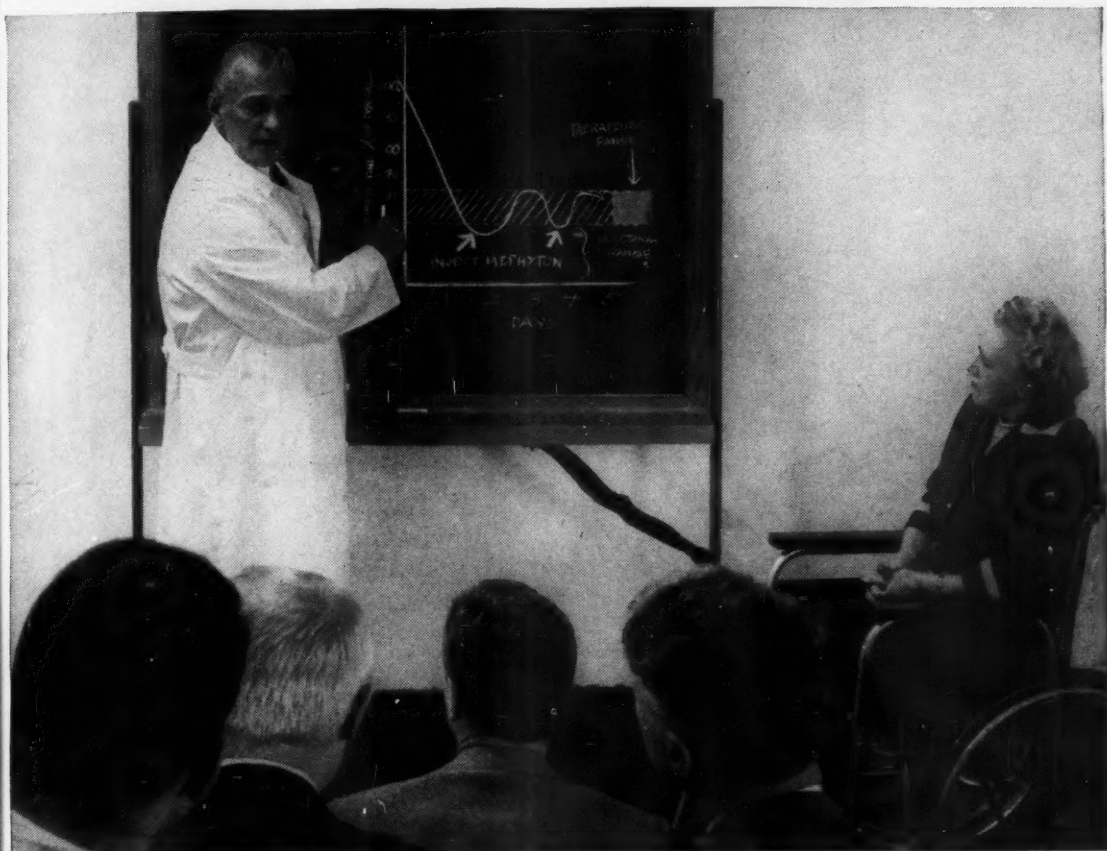


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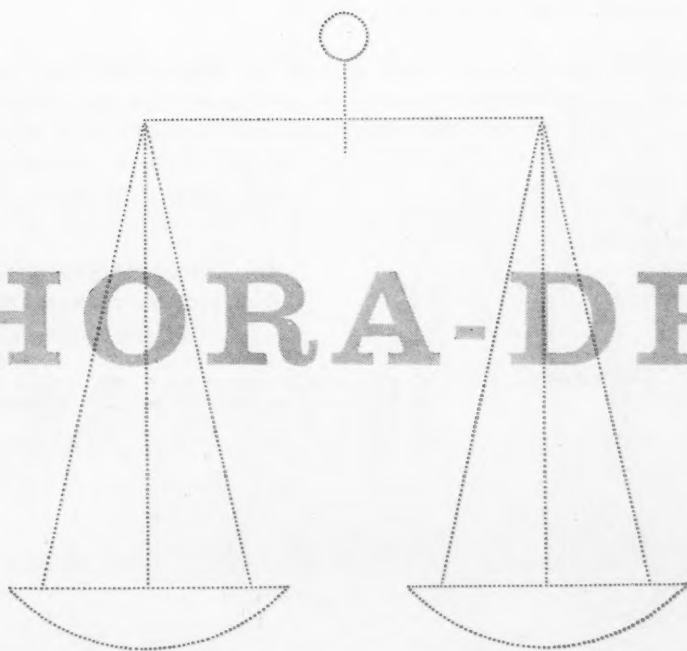
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2. Gitman, L., and Koplowitz, A.: N. Y. St. J. Med. 50:2823, 1950.
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5. Ross, J. W.: J. Nat. M. A. 43:20, 1951; 45:223, 1953.

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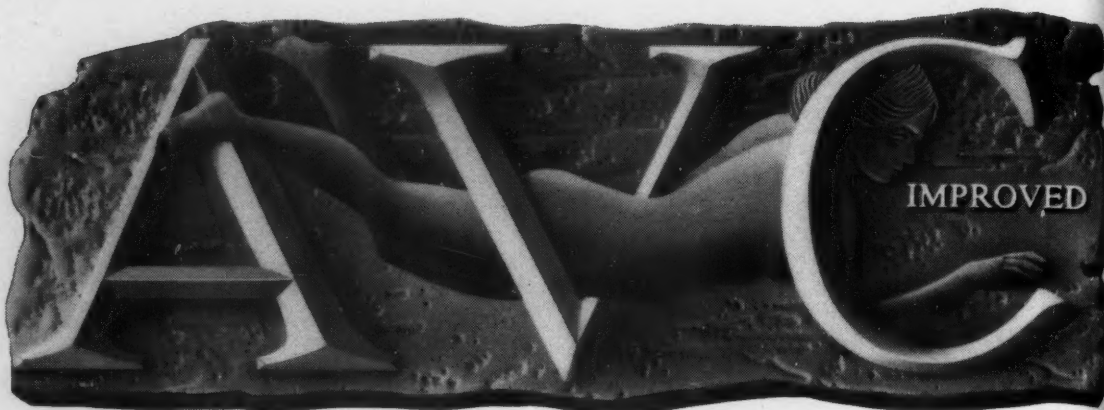
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vitamin-mineral combination

Prescribed early in pregnancy, NATABEC Kapseals get your patients off to a good nutritional start—help keep vitamin-mineral intake up to meet the demands of increased nutritional needs. NATABEC Kapseals provide iron and calcium, plus 12 other important vitamins in a formulation

expressly designed to protect the health of both mother and child.

DOSAGE: As a dietary supplement during pregnancy and lactation, one or more Kapseals daily. Available in bottles of 100 and 1,000.



PARKE, DAVIS & COMPANY

DETROIT, MICHIGAN

Step by Step

Therapy Advances

The latest advance in the
treatment of anemia is

A series of red blood cells, some appearing normal and others slightly irregular, arranged in a horizontal line above the product name.

Roncovite

THE CLINICALLY PROVED COBALT ANTIANEMIC

is advance in anemia therapy is the unique
lity, possessed only by cobalt, to stimulate
bone marrow. With Roncovite, patient
well-being naturally accompanies rapid and
parallel increases in RBC's and hemoglobin.

"These studies show that oral cobalt therapy
can stimulate erythropoiesis . . ."

—Gardner, F. H.: *J. Lab. & Clin. Med.* 41:56 (Jan.) 1953.

"... 57 of the 58 [pregnant] patients (98.2 per
cent) maintained or improved their hemoglobin
[with Roncovite] . . ."

—Holly, R. G.: *Obst. & Gynec.* 5:562 (April) 1955.

With Roncovite . . . "most patients felt an in-
creased sense of well-being when hemoglobin
levels were elevated."

—Hill, J. M.; LaJous, J., and Sebastian, F. J.: *Texas J. Med.* 51:686 (Oct.) 1955.

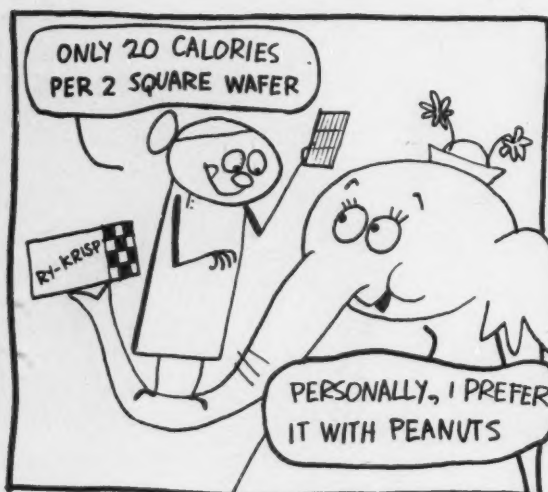
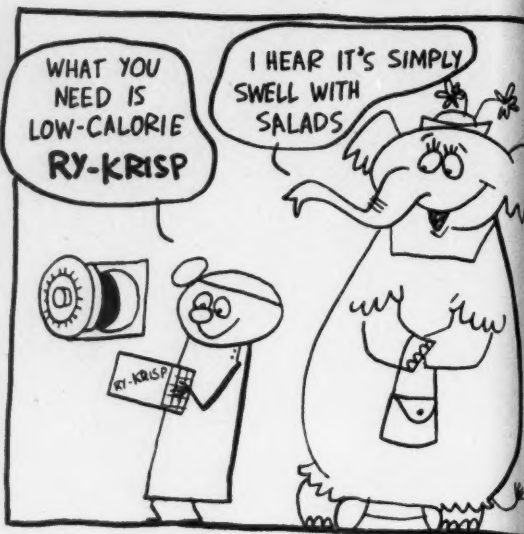
SAGE

One tablet after each meal and at bedtime. Children
1 year or over, 0.6 cc. (10 drops); infants less than
1 year, 0.3 cc. (5 drops) once daily diluted with
water, milk, fruit or vegetable juice.

ROYD BROTHERS, INC.

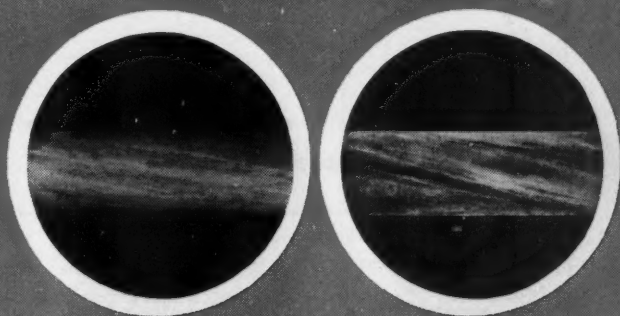
CINCINNATI 13, OHIO

"IN THE INTEREST OF MEDICINE SINCE 1870"



DOCTOR, RY-KRISP'S LOW CALORIE CONTENT HELPS EXPECTANT MOTHERS AVOID EXCESS WEIGHT

Photomicrography shows why D & G gut is stronger— more flexible



D & G gut

Photomicrograph* shows smooth surface of D & G SURGICAL GUT with no fraying or roughness. The soft matte finish prevents knots from slipping. No winding to size. Full natural strength is preserved.

*Medium chromic gut, 5-0; light field method; 106 x

Another leading gut

Photomicrograph* detects surface fraying and roughness. This gut was ground to size. It appears uniform to the naked eye, but the powerful camera lens shows imperfections which may cause weakness when a knot is tied.

D & G gut

Photomicrograph** shows firm, even cohesion of plies—twisted into strands before chromicizing—for greater flexibility. Natural collagen firmly bonds the plies—holds the twist. This results in greater knot strength under stress.

**Medium chromic gut, 00; dark field method; 27 x

Another leading gut

Photomicrograph** detects separate plies in this gut. Here each ply was chromicized before twisting into suture strand. This process limits natural bonding—lowers flexibility and tensile strength—encourages fraying.

Photomicrography shows what
the hand cannot feel

Photomicrographs (unretouched) by E. J. Thomas,
Stamford Laboratory, Research Division of American
Cyanamid Company, Stamford, Connecticut.

DAVIS & GECK
A UNIT OF AMERICAN Cyanamid COMPANY

WATERBURY D&G CONNECTICUT

ADVANCING WITH SURGERY

& Gyn

this is premenstrual tension...

| ITS CAUSES | ITS EFFECTS |
|--|--|
| <p>(a) periodic overproduction of pituitary antidiuretic hormone (ADH) leading to increased antidiuretic activity</p> <p>(b) psychogenic factors, concomitants of menstruation</p> | <p>abnormal water retention</p> <p>electrolyte imbalance</p> <p>disturbed carbohydrate metabolism (hypoglycemia)</p> <p>nervous system lability</p> |
| ITS SYMPTOMS | ITS EFFECTIVE TREATMENT |
| <p>weight gain • abdominal bloating breast tenderness</p> <p>weakness and fatigue mental dullness • depression</p> <p>vertigo • irritability anxiety • palpitation</p> <p>abdominal pain thigh pain • headache</p> | <p>PAMBROMAL</p> <p>Each tablet contains:</p> <ul style="list-style-type: none"> • Pamabrom (to neutralize the action of ADH) 50 mg. • Dextro-amphetamine sulfate 2.5 mg. (to elevate the mood) • Carbromal (to relax tension) 130 mg. • Salicylamide (to relieve pain) 250 mg. |

Whittier

WHITTIER LABORATORIES • CHICAGO 11, ILLINOIS

this is **PAMBROMAL...**

a new and specific
treatment for
premenstrual tension...

| 1. neutralizes the antidiuretic hormone | | | |
|---|-----------|-----------|-----------|
| | Subject 1 | Subject 2 | Subject 3 |
| Diuresis without pamabrom | 106 cc. | 275 cc. | 210 cc. |
| Diuresis with pamabrom (100 mg.) | 950 cc. | 980 cc. | 1200 cc. |

This is how pamabrom (an ingredient of Pambromal) promotes diuresis. Subjects were given 1000 cc. of water and injected with antidiuretic hormone (pitressin). When pamabrom was administered, the water-retaining effect of the antidiuretic hormone was almost completely neutralized.

(Bickers, W., and Woods, M.: New England J. Med. 245: 453, 1951)

2. controls nervous system lability

Pambromal contains both dextro-amphetamine sulfate and carbromal, a reliable sedative. In addition to controlling fluid retention, Pambromal thus provides efficient sedative and antidepressant actions. Irritability, anxiety, and fatigue are counteracted. Tensions are relaxed and a sense of cheerful well-being is established.

3. relieves pain more effectively

Pambromal contains salicylamide, a time-tested and proven analgesic considerably more potent than other salicylates.

controls...fluid retention...anxiety-tension...pain...

PAMBROMAL[®] TABLETS

Bottles of 24 and 100.



The preferred hematinic
with **PEPTONIZED** iron

LIVITAMIN®



Peptonized iron is virtually predigested—better absorbed, better utilized and less toxic than ferrous sulfate. Anemias refractory to other forms of iron will often respond promptly to Livitamin therapy.

The Livitamin formula, containing the B complex, provides integrated therapy to correct the blood picture, and to improve appetite and digestion.

Each fluidounce contains:

| | |
|---|----------|
| Iron peptonized. | .420 mg. |
| (Equiv. in elemental iron to 71 mg.) | |
| Manganese citrate, soluble | .158 mg. |
| Thiamine hydrochloride | 10 mg. |
| Riboflavin | 10 mg. |
| Vitamin B ₁₂ (crystalline) | 20 mcg. |
| Niacinamide | 50 mg. |
| Pyridoxine hydrochloride. | 1 mg. |
| Pantothenic acid | 5 mg. |
| Liver fraction I | 2 Gm. |
| Rice bran extract | 1 Gm. |
| Inositol | 30 mg. |
| Choline | 60 mg. |



THE S. E. MASSENGILL COMPANY

Bristol, Tennessee

New York

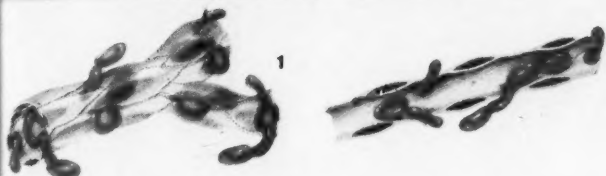
Kansas City

San Francisco



95% FETAL SALVAGE

with HESPER-C



1 Red blood cells escaping from a capillary under abnormal conditions of capillary fragility.



2 Bleeding into the decidua basalis results from increased permeability of the uterine capillaries. The decidua then splits; a decidual hematoma is formed which leads to premature separation of the normally implanted placenta.



HESPER-C

makes the difference

the original synergistic nutritional supplement for capillary fragility, is recommended as an integral part of any regimen for fetal salvage.¹ Maintaining capillary integrity during the critical months guards against abruptio placentae.² In 100 patients whose 420 previous pregnancies resulted in 95% fetal wastage, the addition of HESPER-C to current therapy completely reversed the figure and resulted in 95% fetal salvage.³

Remember Rx HESPER-C along with your usual therapy—it makes the difference.

Maintain the integrity of the capillaries throughout pregnancy.

on your

prescription

only

Now available, convenient New HESPER-C LIQUID.

HESPER-C provides hesperidin concentrate, 100 mg., and ascorbic acid, 100 mg., per capsule and per teaspoonful (5 ml.). DOSAGE: 6 capsules or teaspoonfuls or more per day for the first week. Then 4 capsules or teaspoonfuls daily. SUPPLIED: Liquid in bottles of 4 oz. and 12 oz. Capsules in bottles of 100 and 1000.

REFERENCES: 1. Dill, L. V.: Med. Ann. of D. of C., 23:667, 1954. 2. Greenblatt, R. B.: Obst. and Gyn., 2:530, 1953. 3. Javert, C. T.: Obst. and Gyn., 3:420, 1954.

The film "CLINICAL ENZYMOLOGY" is now available for showing at medical meetings upon your request. And be sure to watch for the MED-AUDIOGRAPHS, a series of recorded clinical discussions.



PRODUCTS OF ORIGINAL RESEARCH

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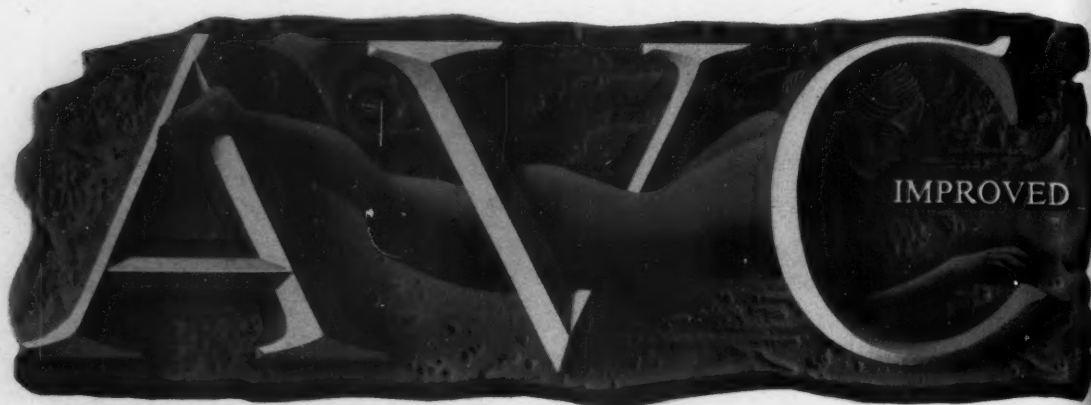
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THE NATIONAL DRUG COMPANY PHILADELPHIA 44, PA.

The CLASSICAL *Vaginal Therapeutic*



UNIQUE WITH 9-AMINOACRIDINE,
the nonirritating, broad-spectrum, stable bactericidal agent.
Effective where organisms have become resistant to other drugs.

AVC Improved has been accepted, and in ever-expanding use for over 12 years,
as the most comprehensive therapy in:

Trichomonal Leukorrheas • Monilial and Nonspecific Vaginitis • Cervicitis • Postpartum Hygiene • Pre- and Postcauterization, Coagulation, Conization and other Vaginal Surgery

AVC Improved provides: Broad-spectrum, sustained vaginal pathogen killing power because the remarkable synergism of 9-aminoacridine and sulfanilamide effects the actual destruction of the inhibitors of maximum bactericidal action. Surface-active, spreading, penetrating agent; buffered vaginal pH; nutrient for normal vaginal flora; mucus digestion; immediate relief of odor and itching; restoration of vaginal mucosa, by actively promoting tissue repair and granulation.

AVC Improved is a cream containing 0.2% 9-Aminoacridine Hydrochloride, 15% Sulfanilamide, 2% Allantoin, in a water-miscible base buffered to approximately pH 4.5.



SUPPLIED: 4 oz. tubes with or without applicator. ADMINISTRATION: An applicatorful of AVC Improved should be introduced high into the vagina twice daily, upon arising and at bedtime.

PRODUCTS OF ORIGINAL RESEARCH



THE NATIONAL DRUG COMPANY PHILADELPHIA 44, PA.

“... may be unique as a wide-spectrum antimicrobial agent that is bactericidal, relatively nontoxic, and does not invoke resistant mutants.”¹

Furadantin[®]

BRAND OF NITROFURANTOIN

in acute and chronic pyelonephritis, cystitis, prostatitis

Percentage of Effectiveness of Furadantin Against Various Strains of Bacteria in Vitro

| | Aerobacter aerogenes | Proteus sp. | Paracolo- bactrum sp. | Micro- coccus pyogenes | Strepto- coccus pyogenes | Esche- richia coli | Pseudo- monas aeruginosa |
|---------------------|-------------------------|----------------|-----------------------------|------------------------------|--------------------------------|--------------------------|--------------------------------|
| Furadantin | 82.1 | 66.6 | 31.2 | 91.9 | 93.9 | 60.0 | 13.3 |
| Antibiotic A | 71.4 | 55.5 | 25.0 | 93.5 | 96.9 | 66.0 | 26.6 |
| Dihydrostreptomycin | 14.2 | 25.9 | 12.5 | 38.7 | 27.2 | 28.0 | 6.6 |
| Antibiotic B | 3.5 | 0 | 0 | 66.1 | 63.6 | 0 | 2.2 |
| Penicillin | 3.5 | 0 | 0 | 27.4 | 39.3 | 0 | 0 |
| Antibiotic C | 14.2 | 7.4 | 18.7 | 46.7 | 72.6 | 22.0 | 11.1 |

ADAPTED FROM PERRY²

Furadantin's "high degree of effectiveness against bacteria responsible for urinary tract infections is brought out by this study."²

Furadantin dosage—simple and safe: Average adult dose is 100 mg., q.i.d., (at mealtime, and on retiring, with food or milk). Average daily dosage for children is 5 to 7 mg./Kg. in four divided doses.

SUPPLIED: Tablets, 50 and 100 mg., bottles of 25 and 100.

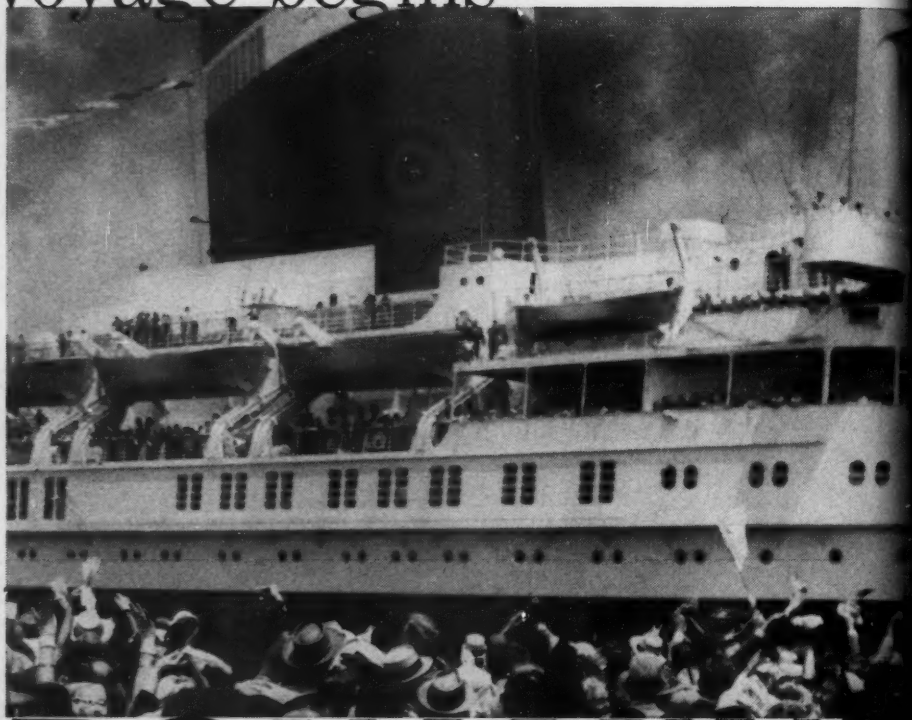
Oral Suspension, 5 mg. per cc., bottle of 118 cc.

REFERENCES: 1. Waisbren, B. A., and Crowley, W.: A.M.A. Arch. Int. M. 95:653, 1955. 2. Perry, R. E., Jr.: North Carolina M. J. 16:567, 1955.

NITROFURANS—A NEW CLASS OF ANTIMICROBIALS—NEITHER ANTIBIOTICS NOR SULFAS

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LABORATORIES

Bon Voyage begins



with

BONAMINE

BRAND OF MECLIZINE HYDROCHLORIDE

longest-acting motion-sickness remedy' ➡ effective in low dosage ➡ controls various symptoms of motion sensitivity in minutes ➡ one dose often prevents motion sickness for 24 hours ➡ as safe as a placebo' ➡ BONAMINE TABLETS, scored, tasteless, 25 mg ➡ BONAMINE CHEWING TABLETS, pleasantly mint flavored, 25 mg.

1. Report of Study by Army, Navy, Air Force Motion Sickness Team: J.A.M.A. 160:755 (March 3) 1956. *Trademark



PFIZER LABORATORIES, Division, Chas. Pfizer & Co., Inc., Brooklyn 6, N. Y.

when prescribing a diaphragm



Ortho Kit



A MARKED ADVANCE *in* *Obstetrical Sedation*

Injection PHENERGAN Hydrochloride meets advanced aims in sedation for labor and childbirth. In a study of 300 obstetrical patients given PHENERGAN with meperidine, Carroll and Hudson¹ report:

- Predictable sedation
- Decreased apprehension
- Easier and shorter labor
- Potentiated hypnotic and analgesic action of meperidine
- Lowered incidence of nausea and vomiting
- Reduced requirement of anesthetic for delivery
- Absence of untoward reactions on mother and infant

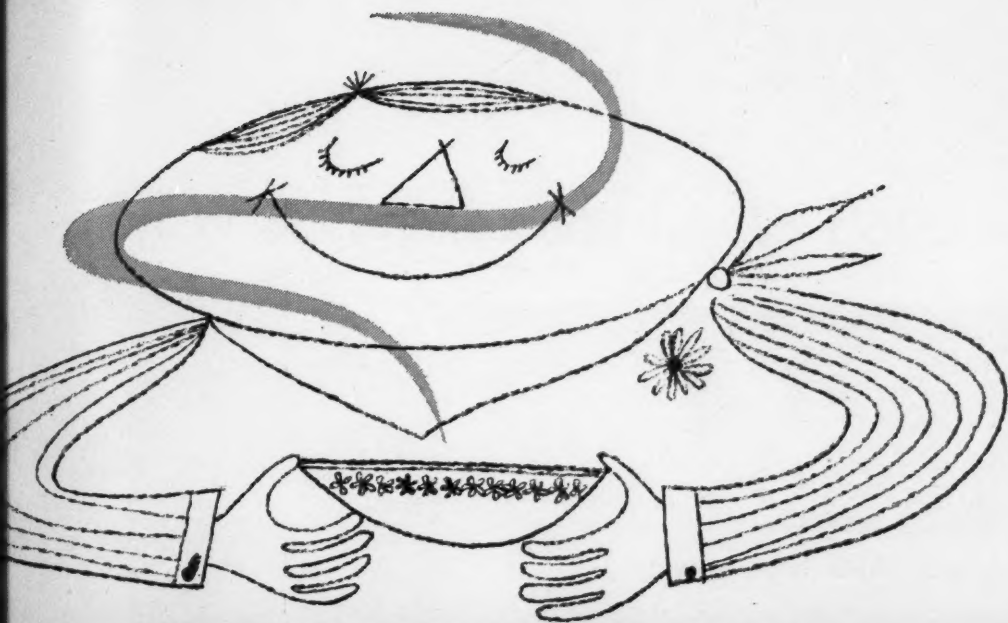
Supplied: Injection PHENERGAN Hydrochloride, vials of 10 cc.; each cc. contains 25 mg. of PHENERGAN Hydrochloride in Water for Injection U.S.P., suitable for intramuscular or intravenous use. Also available: PHENERGAN Hydrochloride Tablets of 12.5 or 25 mg., bottles of 100. PHENERGAN Hydrochloride Syrup, bottles of 1 pint; each 5-cc. teaspoonful contains 6.25 mg. of the salt.

1. Carroll, J.J., and Hudson, P.W.: *Canad. Anaes. Soc. J.* 2:340 (Oct.) 1955.

NEW
Injection
PHENERGAN[®]
HYDROCHLORIDE
Promethazine Hydrochloride



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salt-free needn't mean flavor-free

DIASAL is enthusiastically endorsed by low-salt dieters for the zest and flavor it gives to pallid, sodium-restricted meals. So closely does it match the appearance, texture and taste of table salt that patient adherence to your diet instructions is virtually assured.

DIASAL contains only potassium chloride, glutamic acid and inert ingredients...no sodium, lithium, or ammonium. It may be used safely for extended periods, both at the table and in cooking. Because of its potassium, DIASAL may be a valuable prophylactic against potassium depletion.

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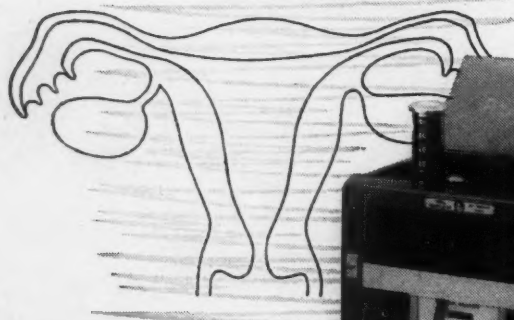
packaging: available in 2-ounce shakers and 8-ounce bottles.

Send for liberal supplies of testing samples and low sodium diet sheets for your patients.

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E. FOUGERA & COMPANY, INC.
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**Whether testing
to determine tubal patency**

**or repeating insufflation
to improve patency**



the new

KIDDE KYMO INSUFFLATOR

provides precise records of pressure variations

Oscillation patterns are easy to read and compare from rectangular graphs. Accuracy is assured by positive electrical control of graph during insufflation.

SAFE AND SIMPLE The Kidde Kymo Insufflator is charged in seconds from a disposable, hermetically sealed cartridge of CO₂. Automatic controls limit the quantity of gas released into the tubes to 100 cc. Maximum pressure is limited by gravity controls to 200 mm. Hg. Rate of flow for each patient is regulated by a single finger-tip control and constantly revealed by the Flow Meter. Pure, filtered carbon dioxide is promptly absorbed by the patient—with no risk of emboli.

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*Ask your dealer to
demonstrate or write
for information to*

KIDDE MANUFACTURING COMPANY

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Kidde, Trademark Reg. U.S. Pat. Off.

The new model
KIDDE KYMO INSUFFLATOR
is compactly designed
and portable.

Weight—25 lbs.

Size—8" x 11" x 17"

***The most completely
safe instrument for tubal
insufflation available***

NEW **SEAMLESS** Lacta Pads



EFFICIENT AID IN POST-NATAL CARE... A CONVENIENCE YOUR PATIENTS APPRECIATE

Hundreds of maternity departments have already adopted these wonderfully practical pads to solve the problem of excess lactation. Depend on your hospital to supply new Lacta Pads—an extra nicety that smooths your practice. Check these advantages:

WHY DOCTORS LIKE THEM

No pressure. Prevent retracted or cracked nipples. Reduce care.

Suited to professional technique. Ideal for applying medication.

Ideally designed and made to solve the excess lactation problem.

Assure greater patient comfort and satisfaction.

Samples promptly available on request. Simply jot it on your prescription form.

WHY PATIENTS LIKE THEM

Made of soft, non-irritating non-allergenic cotton. Highly absorbent and retentive.

Naturally, sensibly contoured. Full 3¼" in diameter.

Outside is non-absorbent; sealed circumference ring.

Full protection of clothing and appearance—no revealing lines.

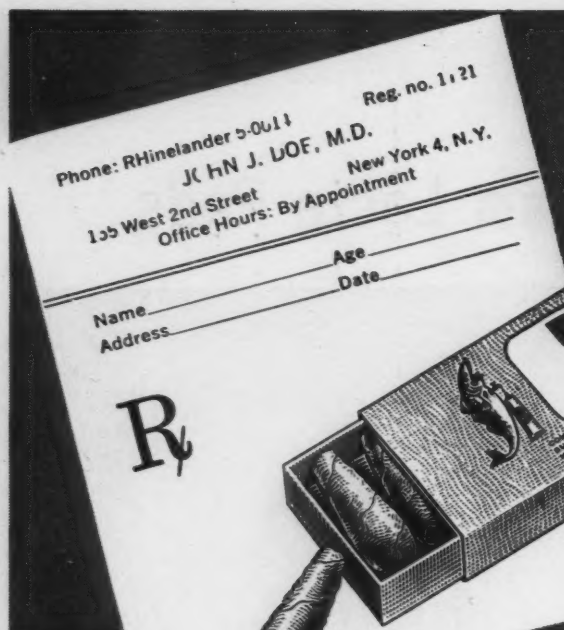
Easy to insert without assistance. Disposable.

Surgical Dressings Division

THE SEAMLESS RUBBER COMPANY

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*prescribe a full measure
comfort for anorectal patients with*

DESITIN

hemorrhoidal **SUPPOSITORIES**
with cod liver oil

In boxes of 12
foil-wrapped
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samples
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DESITIN SUPPOSITORIES quickly soothe, protect, lubricate the distressed anorectal mucosa to provide.....

- gratifying comfort in hemorrhoids (non-surgical)
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How vital to their happiness... the mother's health ➤
 With health, she can meet buoyantly and capably
 the demands of her family and her community. ➤
 Upon her health and vitality rests the happiness of
 her family. She, in turn, depends upon the knowl-
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 being... especially on his advice on scientific methods
 of child-spacing. What more rewarding way for
 the doctor to expend his skill than in the perpetu-
 ation of the happy, healthy family . . . Hence, the
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AVAILABLE AT ALL LEADING PHARMACIES • KOROMEX JELLY, CREAM AND DIAPHRAGM COMPACT
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Safety First

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The first thought of every physician during the prenatal period is the safety of the patient.

The first choice of the physician for an agent to control nausea and vomiting will be EMETROL® when he considers the following advantages:

1. EMETROL does not contain barbiturates, bromides, antihistamine compounds, or any other drugs likely to induce untoward effects.
2. EMETROL has been shown to be effective in nausea and vomiting in controlled clinical studies.¹⁻³
3. EMETROL is so palatable that most patients will take it readily.
4. EMETROL works quickly, often bringing relief with the first dose.

SAFE

EMETROL®

(Phosphorated Carbohydrate Solution)

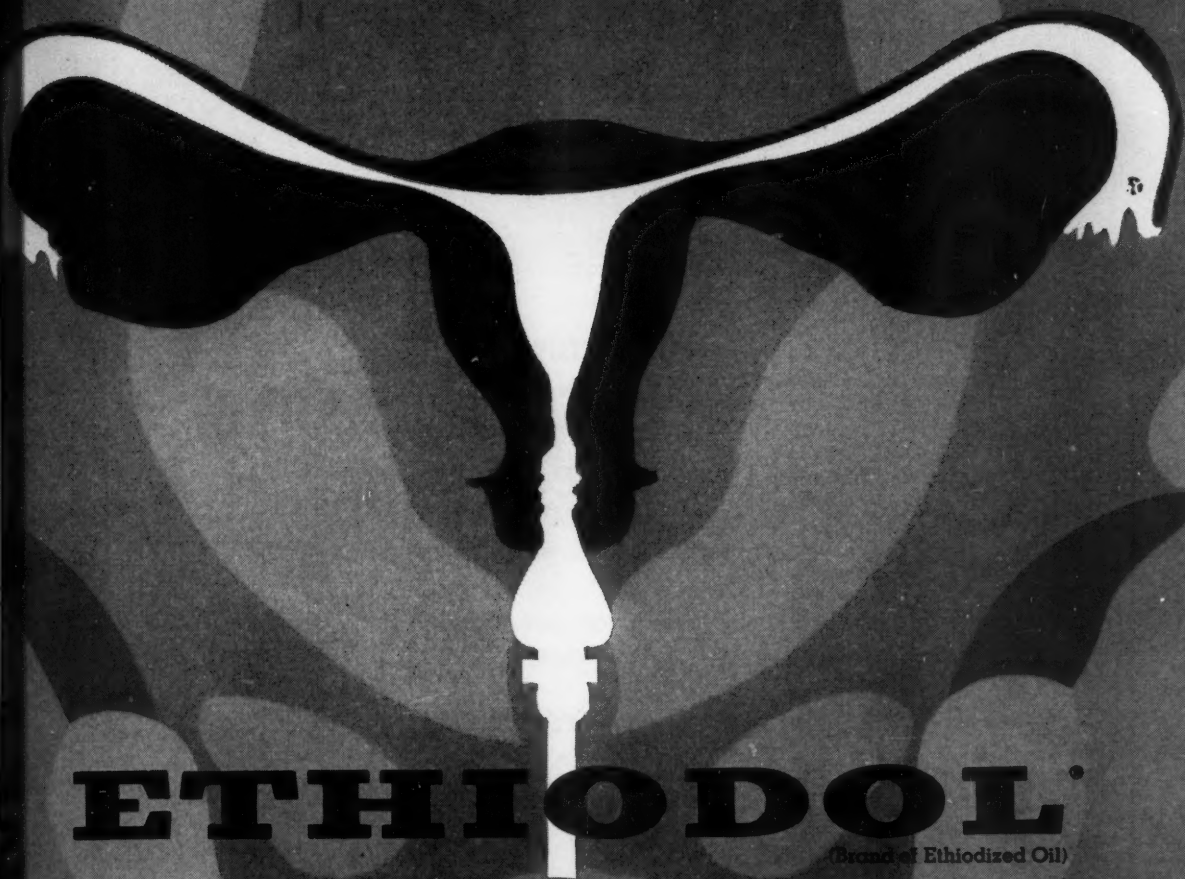


1. Crunden, A. B., Jr., and Davis, W. A.: Am. J. Obst. & Gynec. 65:311, 1953.
2. Bradley, J. E., et al.: J. Pediat. 38:41, 1951.
3. Tebrock, H. E., and Fisher, M. M.: M. Times 82:271, 1954.

Kinney

KINNEY & COMPANY, INC.
COLUMBUS, INDIANA

advantages you want in hysterosalpingography...



ETHIODOL®

(Brand of Ethiodized Oil)

LIPIODOL® diagnostic with free-flowing viscosity

low viscosity for easier administration and free passage through narrow or strictured tubes or openings.

excellent radiopacity provides films as clear as with LIPIODOL for dependable diagnosis.

optimal absorption—completely absorbed usually within 45 days. Permits 24-hour film.

minimal patient discomfort—painless on contact with peritoneum. Bland, non-toxic and nonirritating.

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CHEMICAL DISINFECTION
OF SHARP SURGICAL INSTRUMENTS

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B-P FORMALDEHYDE GERMICIDE to...


contains HEXACHLOROPHENE (G-11*)

KILL vegetative pathogens and spore formers within
5 minutes.*

KILL the spores themselves within 3 hours.*

KILL tubercle bacilli within 5 minutes.*

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SUGGESTION! B-P CONTAINERS
are all especially designed
for convenience in con-
junction with the use of
B-P GERMICIDE.

Used as directed, it will not injure keen cutting edges, points of hypodermic and suture needles, scissors and other 'sharps' . . . nor rust, corrode or otherwise damage metallic instruments.

IT'S THE ECONOMICAL ANSWER towards keeping annual costs for solutions and instrument replacement and repairs at a minimum. May be used repeatedly if kept undiluted and free of foreign matter.

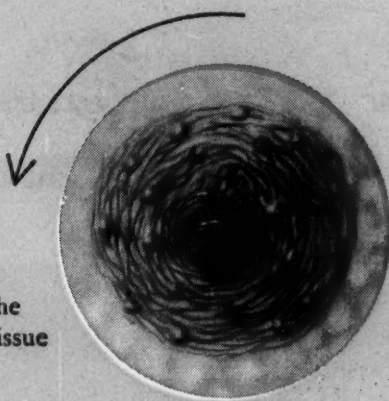
*Comparative chart sent on request

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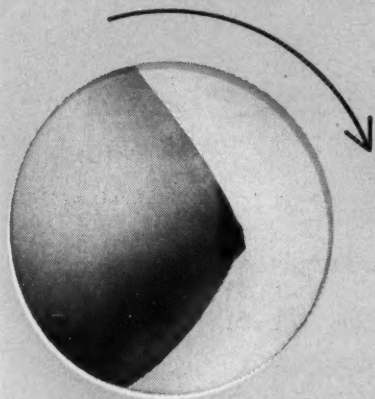
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FISSURED NIPPLE THERAPY

The use of White's Vitamin A & D Ointment soothes and softens the fissured nipple, promotes tissue regeneration.



WHITE'S VITAMIN A & D OINTMENT

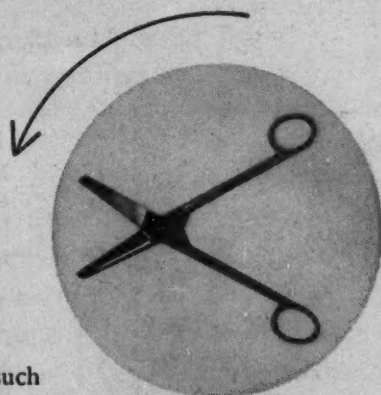


NIPPLE ROUTINE

—a valuable and simple prophylactic measure against drying, fissuring and erosion.

AFTER EPISIOTOMIES

As a post-surgical dressing, White's Vitamin A & D Ointment provides comfort for the patient and encourages rapid healing.



Specify White's Vitamin A & D Ointment also in such conditions as burns, diaper rash, chafing, indolent ulcers.

Recommend the 1½ or 4 oz. tubes; the 1 lb. or 5 lb. jars.



WHITE LABORATORIES, INC./KENILWORTH, NEW JERSEY

New Effectiveness

...for VAGINITIS:



MILIBIS®

Vaginal Suppositories

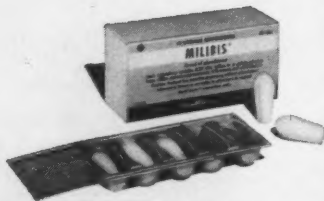
—soft and pliant as a tampon—white, odorless, non-staining—the suppositories bring new ease and new effectiveness to treatment of vaginitis.

ELIMINATE SMEAR EXAMINATIONS*

Milibis vaginal suppositories are effective in trichomonad, Candida (monilia) as well as mixed and bacterial infections—thus laboratory identification of the offending organism is unnecessary.

THERAPEUTIC REGIMEN IS SHORT AND SIMPLE

A total of only 10 suppositories (one inserted every other night) has given a remarkable rate of cure of over 90 per cent in two large series of cases. Milibis vaginal suppositories are easily inserted high into the vagina and form a tenacious film which coats the cervix and rugae, killing pathogens on contact. Non-staining, well tolerated.



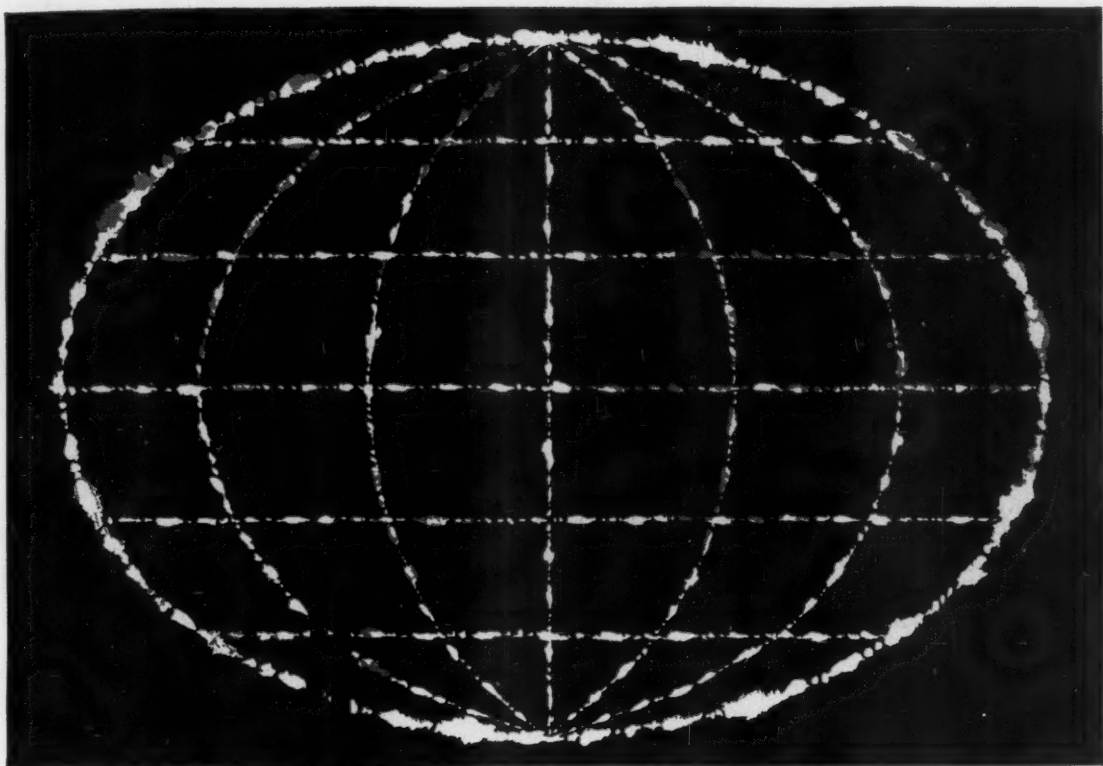
SUPPLIED: BOXES OF 10

*Except when gonorrheal infection is suspected.

Winthrop LABORATORIES New York 18, N.Y.

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More Effective Intravenous Anesthetic



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PENTOTHAL® Sodium

(Thiopental Sodium for Injection, Abbott)

605178

May, 1956

Page 47

for the treatment of

- AMENORRHEA
- FUNCTIONAL UTERINE BLEEDING
- HABITUAL ABORTION
- LOBULAR HYPERPLASIA
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Avoids pain and inconvenience of injection . . . insures better patient cooperation than any other dosage form.

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Response is more predictable than with oral, or buccal and sublingual therapy.

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Cost is low in terms of greater patient benefits.

"Colprosterone" Vaginal Tablets—Brand of progesterone U.S.P. presented in a specially formulated base to insure maximum absorption and utilization.

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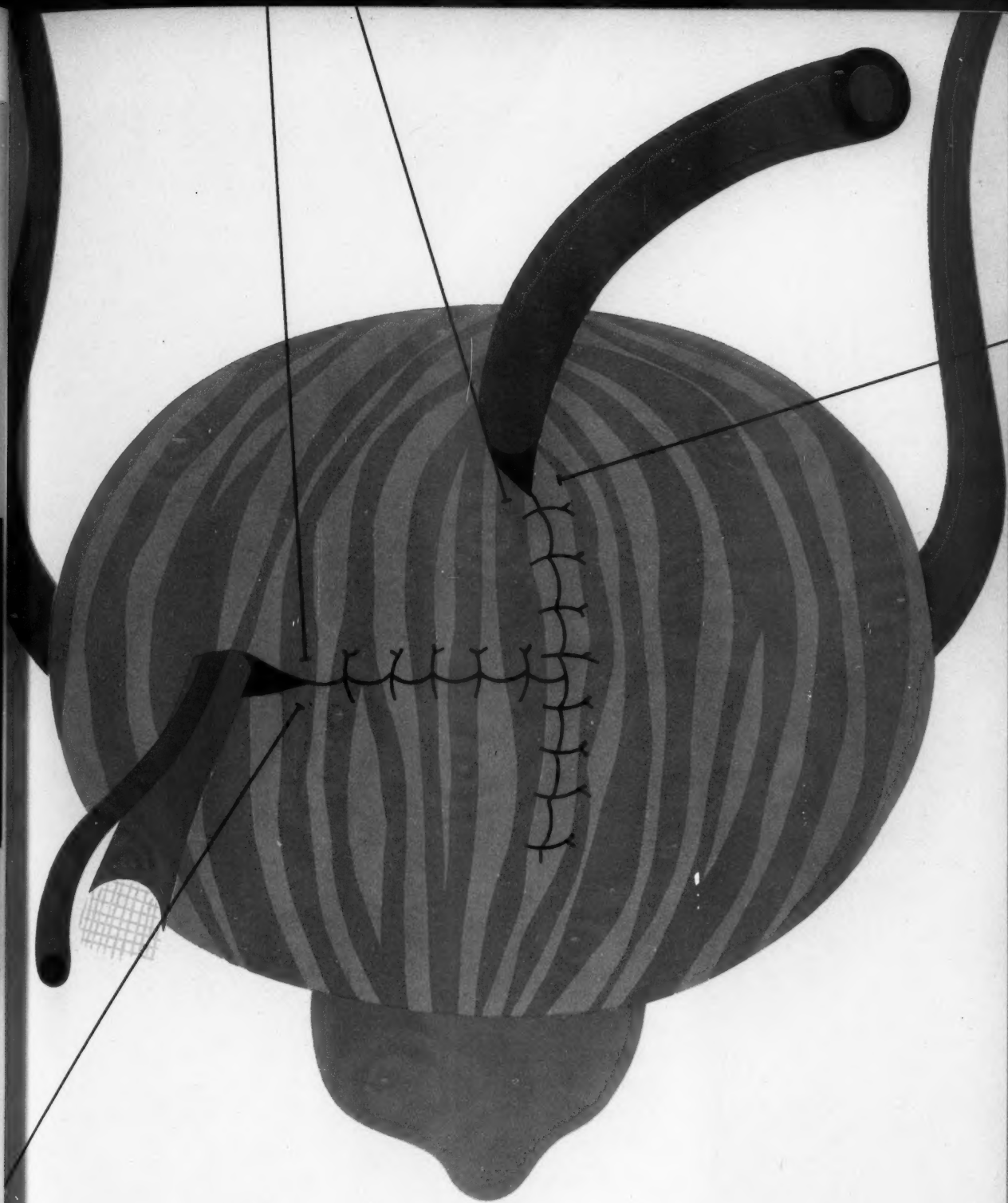
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A Laboratory and Clinical Report on Adrenosem® Salicylate

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History

The first investigation of a hemostat with an action comparable to Adrenosem Salicylate was made by Derouaux and Roskam¹ in 1937. They reported that an oxidation product of adrenalin, adrenochrome (which has no sympathomimetic properties), has prompt hemostatic activity.

It was further found that various combinations of adrenochrome, notably the oxime and semicarbazone, produced stable solutions. But, these were so slightly soluble that sufficient concentration could not be obtained for practical therapeutic use. By combining these adrenochrome compounds in a sodium salicylate complex a stable, soluble form can be obtained. This complex has been given the generic name, carbazochrome salicylate, and is supplied under the trade name Adrenosem Salicylate.

Roskam, in his study entitled "The Arrest of Bleeding,"² enumerates "the drugs whose efficaciousness as hemostatics have been proved by accurate methods in experimental animals and in healthy men as well. . . . One is the monosemicarbazone of adrenochrome [Adrenosem Salicylate]."

Chemistry

Adrenosem Salicylate is a synthetic chemical. The full chemical name is adrenochrome monosemicarbazone sodium salicylate complex.

Pharmacology

Although it is chemically related to epinephrine, Adrenosem Salicylate has no sympathomimetic effects. It does not alter blood components, nor does it affect blood pressure or cardiac rate.²⁻⁷

(* U.S. Patent 2,581,850)

Sherber, in an early study,³ concludes that Adrenosem Salicylate* "is a potent antihemorrhagic factor in those conditions in which the integrity of the smaller vessels is interrupted, and is superior to any similar material that is now available."

He continues, "From our experience it appears that adrenochromazone complex is indicated in preventing vascular accidents incident to hypertension; in maintaining small vessel integrity; in the preoperative preparation where oozing from a vascular bed is anticipated, as in tonsillectomies, adenoidectomies and prostatectomies; and as an adjunct in the treatment of bleeding from such surgical procedures."

Adrenosem Salicylate may be administered simultaneously (but separately) with any type of anesthetic, anticoagulant, or vitamin K and heparin.

A Unique Systemic Hemostat

Clinical investigators²⁻⁷ are in agreement that Adrenosem Salicylate controls bleeding and oozing by decreasing capillary permeability and by promoting the retraction of severed capillary ends. It aids in maintaining normal capillary integrity by direct action on the intercellular "cement" in capillary walls. The interesting work of Fulton⁸ confirms this. Adrenosem Salicylate, since it is not a vasoconstrictor, has no effect on large severed blood vessels and arterioles.

Adrenosem Salicylate is being used both prophylactically and therapeutically in thousands of hospitals, and in virtually every type of surgical procedure. It has also proved most useful in dental surgery.⁷

Owings reported on the use of Adrenosem Salicylate in controlling postoperative adenoid bleeding in 102 cases.⁴ "We have used 2½ mg

($\frac{1}{2}$ ampule) intramuscularly, 15 minutes before anesthesia for children and 5 mg. (1 ampule) for adults." In only one patient did bleeding occur. Three others showed red blood from the nose and mouth. These patients "were then given 5 mg. intramuscularly, with prompt and complete control. We have also noticed that bleeding stopped more promptly on the operating table."

This is a 1% incidence of postoperative bleeding using Adrenosem Salicylate preoperatively, compared to an incidence of 10% postoperative bleeding in all cases taken from previous records, without Adrenosem Salicylate medication.

Peele reports on the use of Adrenosem Salicylate in treating 178 patients with 24 different conditions.⁵ The drug was first used to control postoperative hemorrhage from the adenoid region. He adds: "The results were so dramatic that since that date [1953] Adrenosem Salicylate has been used postoperatively to reduce bleeding from all otolaryngologic and bronchoesophagologic procedures, to treat postoperative hemorrhage from the tonsil and adenoid regions, and to treat selected cases of epistaxis."

The effectiveness of Adrenosem Salicylate in controlling bleeding and oozing in 330 patients is reviewed by Bacala.⁶ "Our experience of the effect of carbazochrome salicylate on 317 surgical indications and 13 obstetricogynecological conditions, has been therapeutically encouraging and successful for the control of capillary bleeding. Foremost among the cases studied were 223 tonsillectomies definitely benefited by this metabolic hemostat, making a diminution of the control incidence of post-tonsillectomy bleeding of 19.8% down to 7%. It has also been found useful in gastro-intestinal bleeding, cataract extraction, epistaxis, incisional seepage, trans-urethral prostatectomy, menometrorrhagias, cervical ooze, antepartum and postpartum bleeding, threatened abortion, and prevention of capillary hemorrhages during hedulin or dicumerol therapy."

Side Effects

All investigators concur that, at recommended dosage levels, Adrenosem Salicylate is free from toxic effects. No cumulative effects

attributable to the drug have been reported.

The only side reaction noted has been a transient stinging sensation in the area of injection when Adrenosem Salicylate is used intramuscularly. As one investigator comments: "The brief discomfort which attends the injection of Adrenosem into the gluteal region has not been a significant problem in children or adults as originally anticipated."⁵

Indications

Idiopathic purpura, retinal hemorrhage, familial telangiectasia, epistaxis, hemoptysis, hematuria.

Postoperative bleeding associated with:
tonsillectomy, adenoidectomy and nasopharynx surgery;
prostatic and bladder surgery;
uterine bleeding;
postpartum hemorrhage;
dental surgery;
chest surgery and chronic pulmonary bleeding.

Dosage

For recommended dosage schedules, please send for detailed literature.

Supplied

Ampuls: 5 mg., 1 cc. (package of 5).
Tablets: 1 mg. S.C. Orange, bottles of 50.
Tablets: 2.5 mg. S.C. Yellow, bottles of 50.
Syrup: 2.5 mg. per 5 cc. (1 tsp.), 4 ounce bottles.

References

1. Roskam, J. and Derouaux, G.: Arch. of Intern. Pharmacodynamie 71:389 (1945).
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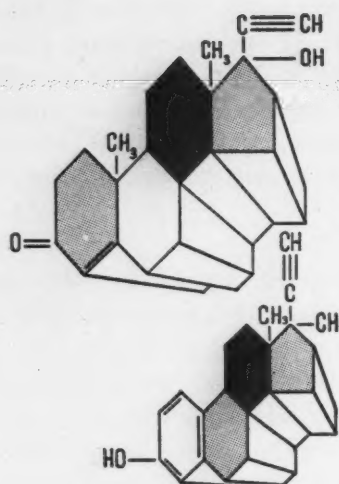
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*Am. J. Obst. & Gynec., 68:1321, 1954.

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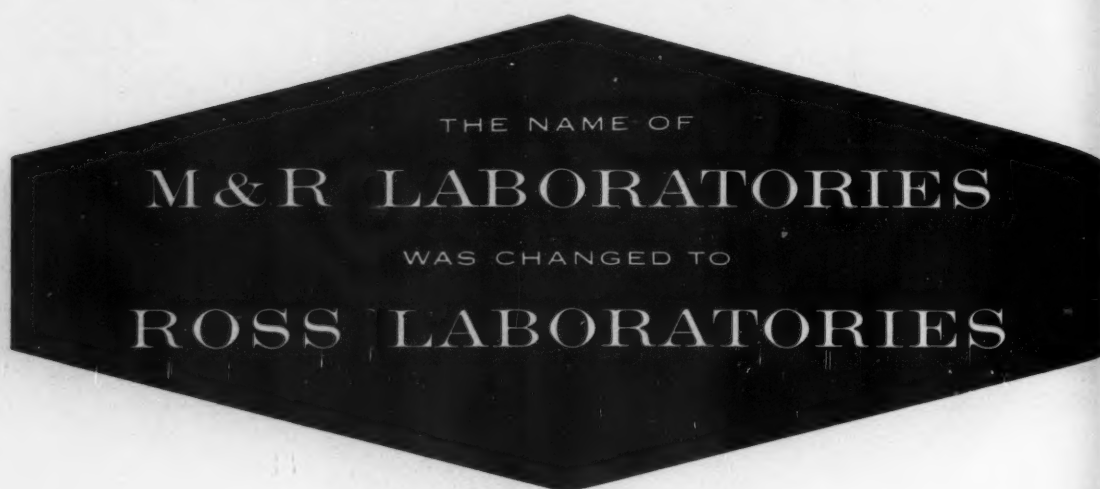
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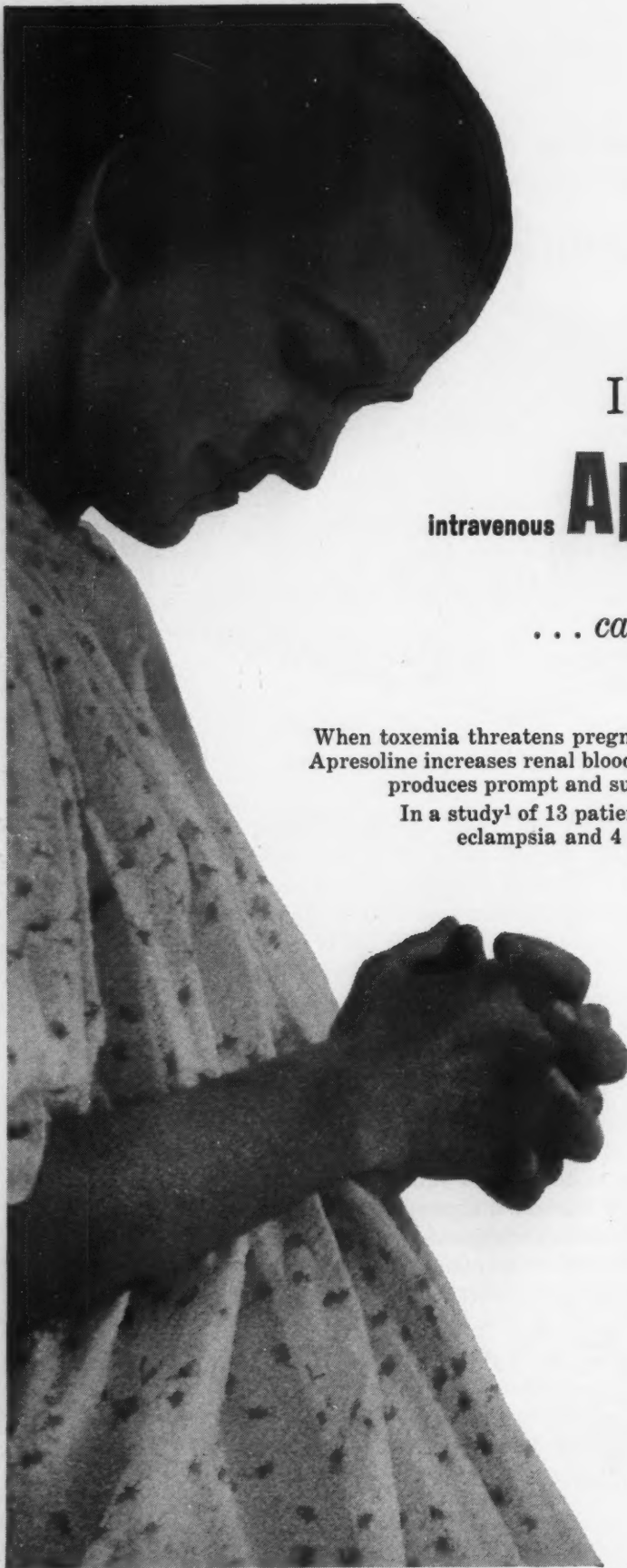
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We believe it incumbent on Ross Laboratories to encourage and to participate in fundamental and applied research in the field of nutrition. The M & R Pediatric Research Conference program will be carried on as the Ross Pediatric Research Conferences. This program is but one instrument for achieving this objective. We shall continue with renewed vigor our efforts to provide means for further enhancement of the practice of medicine for infants and children.

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1. Kistner, R. W.: J. Obst. & Gynec. Brit. Emp. 61:463 (Aug.) 1954.

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References: (1) Hart, F. D., and MacLagan, N. F.: *Brit. M. J.* 1:512 (Mar. 4) 1950. (2) Starr, P., and Liebhold-Schueck, R.: *J.A.M.A.* 155:732 (June 19) 1954. (3) Starr, P.: *Postgrad. Med.* 17:73, 1955.

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1. College Study Report: Population Bulletin 11:45 (June) 1955.
2. Tietze, C., in Dickinson, R. L.: Techniques of Conception Control, ed. 3, Baltimore, Williams & Wilkins Co., 1950, pp. 55-57.

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1. Lund, C.J.: Am. J. Obst. & Gynec. 62:947 (Nov.) 1951.

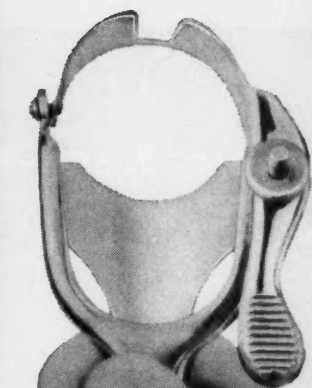
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Hague Mat. Hosp. 1:68 (Sept.) 1948.

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American Journal of Obstetrics and Gynecology

VOL. 71

MAY, 1956

No. 5

*Transactions of the Central Association
of Obstetricians and Gynecologists, Twenty-third Annual Meeting
Columbus, Ohio, October 6, 7, and 8, 1955*

TO CURE SOMETIMES*

Presidential Address

FRANK L. MCPHAIL, M.D., GREAT FALLS, MONT.

OVER twenty-five years ago, a small group of older obstetricians and gynecologists foresaw the need for an organization to stimulate the younger men in the specialty by holding scientific meetings through which the participants could learn from others and teach from their own experience; where they could during leisure hours renew old friendships and make new friends among those with similar interests. In 1929 the Central Association of Obstetricians and Gynecologists held its first meeting in St. Louis. The confidence placed in this young men's organization was well founded. The Central Association has since contributed vitally to the progress of our specialty. Adair² said recently, "I am sure that it has outstripped the dreams of its founders." It is a singular honor, and one for which I am deeply grateful, that you chose me to serve as your president for the year in which the Central Association begins its second quarter century. It seems fitting that at this time we should review the progress of the last twenty-five years, and consider some of the problems of today.

Twenty-five years ago the maternal and infant mortality rates in this country were very high and our position, as compared with other countries, was not enviable. In 1919 a voluntary organization, the Joint Committee on Maternal Welfare, was formed. This was exclusively a medical organization.

*Presented at the Twenty-third Annual Meeting of the Central Association of Obstetricians and Gynecologists, Columbus, Ohio, Oct. 6, 7, and 8, 1955.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

This committee developed most of the plans which were to lower our high mortality rates. In 1929, President Herbert Hoover called the Third White House Conference on Child Health and Protection, at which one of our founders, Dr. Adair, served as Chairman of the Committee on Prenatal and Maternal Care. Dr. E. D. Plass, another founder, was a very enthusiastic supporter of these movements. Many others from the Central Association served on the White House Committee. Ideas, later developed by this White House Conference, had been originally developed by the Joint Committee on Maternal Welfare. This committee was later incorporated in 1934 under the name of the American Committee on Maternal Welfare. The Central Association through its representative was one of the incorporators. One purpose of this new organization was to implement the ideas formulated at the White House Conference, and enlarge them as time and knowledge indicated. One of the important developments of the American Committee was the inauguration of the American Congress on Obstetrics and Gynecology, the first of which was in Cleveland in 1939. There have now been six of these congresses, and members of the Central Association have always carried much of the load. The congresses have served to bring together the professional groups who were interested in improving maternal care. In 1950 the International Congress was held in New York, and from this developed the Geneva Congress of 1954 and the new International Federation of Gynecology and Obstetrics.

Maternal and Infant Mortality Rates.—

At the Third White House Conference in 1930, Adair³ in his Chairman's report challenged the doctors, individually and collectively, to lead a movement to teach parents the value of preconceptional care and create a desire for normal, healthy children; to provide properly trained and educated doctors, nurses, midwives, dentists, and social service workers; and to stimulate communities to provide proper institutions and personnel.

Findley⁴ advised the unification of departments of obstetrics and gynecology in medical schools, staffed by qualified obstetricians and gynecologists. These departments would offer special pathology courses, manikin demonstrations, and clinical clerkships. He urged a more liberal allotment of teaching hours to clinical obstetrics.

Holmes⁵ recommended that teaching institutions provide adequate graduate courses in obstetrics, suggesting that state universities develop courses of the "circuit type" for local practitioners, so that they might improve their methods and keep up to date.

Ehrenfest⁶ emphasized the importance of better prenatal care to more women, and warned that the demand for shorter and more comfortable labors inevitably implies risk for both mother and baby. Interference with pregnancy or labor, he said, should be limited to well-defined indications. Since abortion was responsible for much maternal mortality, he recommended that at least all febrile patients should be hospitalized. Ehrenfest also suggested appropriate changes in birth and death certificates so that more complete and precise information could be obtained.

Kosmak⁷ pointed out deficiencies in the teaching of obstetric nursing. His committee recommended a study of the best ways to prepare, control, employ, and supervise attendants for maternity work.

These outstanding reports, of particular interest to the teacher and practitioner of obstetrics, were published,^{8, 9} and the recommendations, by virtue of mass professional and lay educational efforts, resulted in great reduction of

maternal mortality. In 1929, when hemorrhage, toxemia, and sepsis were the great killers, we thought that a maternal mortality rate of 10 deaths per 10,000 live births was the irreducible minimum. Today, Miller¹⁰ estimates that 60 per cent of our present maternal deaths—5 per 10,000 live births—may be prevented. In the last twenty-five years the death rate from infection, hemorrhage, and toxemia has been greatly reduced. Reported maternal death studies have demonstrated that deaths from heart disease and anesthesia have now assumed a much greater relative importance, a result of that decrease. DeLee¹¹ remarked in 1930, "Heart disease is not sufficiently feared by the general run of practitioners." Recent reports indicate that this statement could well be re-emphasized.

Hersey,¹² in the Michigan Mortality Study, reported a total of 382 maternal deaths for the three-year period from 1950 through 1952. These figures include deaths from both obstetric and nonobstetric causes. The classification is significant.

MICHIGAN MATERNAL MORTALITY STUDY.¹² ALL MATERNAL DEATHS, 1950-1952

| CLASSIFICATION | 382 DEATHS | PER CENT |
|----------------------|------------|----------|
| I. Hemorrhage | 101 | 26.44 |
| II. Infection | 75 | 19.63 |
| III. Toxemia | 73 | 19.11 |
| IV. Heart Diseases | 28 | 7.33 |
| V. Anesthesia | 22 | 5.76 |
| VI. All Other Causes | 83 | 21.73 |
| Total | 382 | 100.0 |

Hemorrhage is responsible for more than 25 per cent of the maternal deaths, according to these reports. Longyear¹³ comments, "Despite the almost universal availability of blood for transfusion, deaths due to hemorrhage remain disconcertingly static. . . . Success here depends upon prompt, adequate therapy. . . . Too little and too late, are reflected too often in failure. . . . Best results are obtained when hemorrhage is anticipated, when blood is available for use should it occur." We still have unnecessary deaths from hemorrhage.

Although in the last twenty-five years scientific and clinical research has added much new information concerning the toxemias, their cause is still unknown. Too often when we do not cure, residual damage remains. Sutton¹⁴ suggests that, "even though the etiology is not known, prevention in this group is the aim." If we are to reduce the deaths from this serious complication, its early signs must be recognized and treatment instituted promptly. We still have unnecessary deaths from toxemia.

Williams¹⁵ emphasizes the importance of educating physicians to the proper use of newer antibiotics, pointing out that deaths from infection will continue until some of the diseases associated with pregnancy are brought under control. He stresses the continued education of the public about the importance of prenatal care and the danger of induced abortion. While deaths have been reduced by better asepsis and the use of antibiotics, it is possible that we should heed recent warnings in regard to the development of resistant strains of bacteria. They may cause us to lose ground to infection in the coming years. We still have unnecessary deaths from infection.

Recent maternal mortality studies in Michigan¹² and Minnesota¹⁶ indicate that heart disease and anesthesia combined approach infection as important causes of maternal deaths. In heart disease the importance of early and continuous antepartum care cannot be overemphasized. New surgical techniques promise relief from the crippling effect of mitral stenosis, but unless surgery improves the status of the cardiac patient, the outlook must always be regarded as serious. The problem of obstetric anesthesia is largely one of education. The

obstetrician and hospital administrator must accept greater responsibility and, as Ehrenfest warned twenty-five years ago, the patient must be better informed about the danger of anesthesia. We have unnecessary deaths from heart disease and anesthesia.

In the Michigan study, Hersey¹⁷ observed that many deaths caused by complications unrelated to pregnancy might have been successfully treated had the patient received adequate prenatal care, with proper consultation. Urging more education of the public to the value of early prenatal care, she suggested that had current knowledge of the management of obstetric complications been utilized, many of the mothers who died would have survived their pregnancies. The time has arrived when we must break down the hodgepodge classification, "all other causes," in order to attack a group which accounts for about 22 per cent of our maternal deaths. We have unnecessary maternal deaths listed under this vague heading.

Much is yet unknown in obstetrics. Over the country as a whole, however, progress of which we are now capable is often impeded because that which is known is not put to practical use. Committees appointed by both state and local medical societies have reported many factors involved in maternal deaths. These reports have been illuminating. Despite the fact that this information has been published there has been in recent years no significant decrease in mortality rates. Your Special Committee on Maternal Death Studies,¹⁸ which reported this morning, was formed to determine if and how these studies could be used more effectively. This critical study should be continued. It has aroused interest outside of this Association. I hope that this interest may culminate in a workshop at the national level, similar to the White House Conferences. Such a conference could be initiated by the American Committee on Maternal Welfare. They have already established a subcommittee^{19, 20} for the purpose of coordinating state and local mortality and morbidity committees at the suggestion of Dr. Philip F. Williams. The American Committee could work in conjunction with the Maternal and Child Health Committee of the American Medical Association to which other interested groups, such as this, could contribute. The American Medical Association is organized so that recommendations agreed upon could be presented to all state and local societies. This would assure more effective application of the recommendations of maternal welfare committees. We can improve the caliber of obstetric practice by the continuous dissemination of knowledge.

Gynecologic Treatment.—

There have been many changes in gynecologic treatment in the past twenty-five years. The uterine suspension once frequently performed is now rarely done and even more rarely scheduled as a planned surgical procedure. Miscellaneous operations on tubes and ovaries are much less frequent. Supravaginal hysterectomy has yielded to total hysterectomy except for rare indications. Pelvic inflammatory disease is seen less often and when seen can usually be treated successfully without operation. The young woman is now given a chance to have children by the removal of fibroid tumors without the removal of the uterus. Methods of repairing relaxations and lacerations have improved. Radiation is rarely used for the treatment of benign bleeding. The approach toward the treatment of endometriosis is now conservative but the syndrome is still too seldom recognized. There are many unsolved problems in the treatment of sterility. Great advances have been made in endocrinology, yet we understand little more of the phenomenon of ovulation than we did twenty-five years ago. As more and more women become wage earners, the problem of dysmenorrhea becomes an important economic factor.

Cancer cannot be controlled until we know the cause. Although scientific and clinical research have added a great deal to our knowledge, our greatest

weapon against cancer is early diagnosis. More professional and lay educational programs are needed so that treatment may be started early. We must rely on early diagnosis, with prompt and thorough treatment, if we are to improve our results. Cytologic techniques have increased the chance for early diagnosis of cancer of the cervix. While the diagnosis and treatment of carcinoma in situ of the cervix are still debatable, research will yield valuable information in the near future. When suspicion is roused, however, a satisfactory biopsy must be obtained. It is possible to take a small biopsy and miss a small carcinoma. When a large biopsy is taken, the physician must assume the responsibility that his pathologist will make many sections of the biopsy before giving a negative diagnosis or before diagnosing noninvasive carcinoma. The effect of radiation therapy may be more accurately followed by combined cytologic study. This information may be of aid in determining the best method of treating carcinoma of the cervix in the individual patient.

There has been little change in the method of treating carcinoma of the endometrium. The diagnosis and treatment of carcinoma of the ovary are still a problem. There has been little advance in the last twenty-five years. Early diagnosis and early treatment by modern surgical methods are giving good results in the treatment of carcinoma of the vulva.

As in obstetrics, much of the progress of which we are capable in gynecologic practice is impeded because that which is known is not put to practical use. We must take the greatest interest in the education of the physician, the patient, and each separate community throughout the country. The time has arrived to devote more time to an educational program in obstetric and gynecologic problems.

Educational Program.—

Any successful educational program must begin with our young people. Norman Cousins²¹ writes: "Education fails unless the Three R's at one end of the school spectrum lead ultimately to the Four P's at the other—Preparation for Earning, Preparation for Living, Preparation for Understanding, Preparation for Participation in the problems involved in the making of a better world."

Our real problem in medicine is neither socialism nor federal aid. Our real problem is the scarcity of good physicians. Every index of our national life shows expansion, yet we turn out relatively few more physicians than we did fifteen or twenty years ago. If all medical societies would take an active interest in high school vocational guidance programs and in the availability of medical schools for those who show a real desire and aptitude for medical education, I am sure that the number of medical students could be increased.

Few trained men endure so prolonged and intensive a training period as those who graduate from a medical school, yet too often the result is a trained technician and an ignorant man. The answer to this problem is rooted somewhere in the premedical education of the student, and this is not a problem that the medical profession can solve by itself. Can it be that we have not thought through the matter of the balance between technical knowledge and liberal education? In medicine, of all fields, can we do less than train the "whole man"? As it is, the intensive training which is required limits the scope and usefulness of the finished product. From the standpoint of an understanding of the relationship between body and mind and of the relationship of the individual to the community, the doctor trained by modern methods is undereducated. Somehow the medical profession must accomplish the impossible. It must push ahead its techniques, knowledge, and skills while rediscovering the individual and the community. The premedical educational program must undergo revaluation.

With each discovery in medicine our technology is expanded, the cost of instruction is increased, and the time of education is prolonged. With the increasing cost of education, both public and private schools feel the "economic pinch." Darley²² says, "All medical educators feel that the basic structures of the existing schools and their educational programs must be properly strengthened through more adequate financing." Some states have too small a population to support a medical school. This increases the tax load for those states supplying this need, and legislators question the wisdom of increasing state taxes in order to educate students from other states. One solution for this tax problem is the regional compact for the support of higher education. The two now in existence, the Southern Regional Education Compact in Higher Education and the Western Interstate Compact for Higher Education, serve as agencies within the region so that a state lacking certain educational facilities may purchase the needed facility from any other state having space in the required field. A state having no medical school may, through the compact agreement, pay an institution in another state an amount sufficient to defray the full cost of education for each student, less the regular tuition.

Once educated, the medical student needs intelligent guidance to assist him in making a choice for further training in some specialized medical field. It is a matter of public safety that many graduates must receive such training. Here, as at the high school level, our medical organizations can be of great help. A wrong choice is almost irrevocable. A physician practicing a specialty for which he is poorly adapted represents a great loss in both "Preparation for Understanding" and "Preparation for Participation." Gardner²³ in reporting a survey of the 1934-1943 graduates from Northwestern University Medical School says: "This survey . . . has produced evidence proving that Obstetrics and Gynecology fails to attract its proportionate share of the more 'talented' young physicians." In this study, a comparison of the findings at Northwestern with that of the trend manifested by graduates from all medical schools was reported. This information, he concludes, ". . . suggests that this same humiliating state of affairs probably exists among all recent graduates, and that it is not unique for Northwestern." He noted, ". . . if the data from Northwestern are fairly representative of the situation in all schools, or in most schools, then the major causes are general; in fact they are fundamental and deep seated. By the same token, corrective measures must be on a general level where they can influence the entire specialty. . . ."

A continuing education must be carried to the physician in general practice. He must be kept aware of new methods and informed as to reasons for failure in treatment. Much of this information can be relayed through the hospital staff meeting, the county society meeting, refresher courses, and formal postgraduate courses. When indicated, the so-called "circuit courses" may eradicate problems in isolated areas. Studies like those carried out in maternal and infant mortality may be broadened to cover other fields. The potential of educational television is still beyond comprehension. Noncommercial educational television is now in the experimental stage. As its value is recognized by the public, it can bring current knowledge directly from the medical school to the physician. A continuing educational program will increase the detection rate and, as a result, raise the cure rate.

Education of the public falls into two categories: the individual as a patient, and the individual as a unit in the community. The patient should recognize the importance of antepartum care and should have enough basic knowledge so that she may judge her physician on merit. She should be aware of accepted treatment procedures for common complications, as well as the signs of serious disease. The individuals who comprise the community should be aware of minimum requirements in hospital facilities. They must know that

equipment is needed and must make certain that it is provided, if specific services are to be offered in that community. A death from hemorrhage cannot be well explained on the ground that facilities for transfusion were not available. The increase in the number of rural hospitals has produced a scarcity in trained personnel. No matter how fine the hospital building may be, it is a dangerous experiment unless adequately staffed. In the interest of safety, rigid requirements must be enforced.

As our knowledge unfolds and as we recognize factors which by practical application tend to be either lifesaving or life-prolonging, we have a new responsibility to society. This responsibility is largely one of education. Important information should be made available to all physicians, to all individuals, and to society as a whole. Educational television could be of great help in accomplishing this objective. If Walt Disney can show the birth of a buffalo in *The Vanishing Prairie*, just think what we might do in informing the public of accepted procedures in medicine.

In obstetrics and gynecology the cure rate in 1955 is much higher than it was twenty-five years ago, though we realize that it would be possible to cure many more if what we now know were more widely applied. But as our cures increase, we must remember that there will always be some who cannot be cured but who can be relieved or comforted.

*Guérir quelquefois
Soulager souvent
Consoler toujours*

—Author unknown¹

At the Saranac Lake Tuberculosis Sanatorium, now closed because there were too few patients to warrant keeping it open, Trudeau's former patients erected a memorial. On one side they inscribed this simple statement: "Those who have been healed in this place have put this monument here, a token of their gratitude. August 10, 1918." On the other side is this quotation, Trudeau's favorite: "To cure sometimes; to relieve often; to comfort always." The author of the maxim is unknown. "Au XVe siècle, on disait: La présence d'un médecin profite beaucoup. Son rôle est de guérir quelquefois, soulager souvent et consoler toujours."^{1*}

"To cure" is defined as to restore to health. While the cure of the patient is at all times our objective, we realize that it cannot always be achieved. In 1637 Descartes²⁴ wrote of medicine: "I am sure that there is no one, even among those who make its study a profession, who does not confess that all that men know is almost nothing in comparison with what remains to be known." This is true in obstetrics and gynecology. Descartes' meaning is not altered or lessened by our increase in knowledge. As we review the obstetrical and gynecological problems of twenty-five years ago and those of today, we realize that there are still many avenues of research open. These must be explored if we are to increase our cure rate.

In 1929 the maternal mortality rate in the United States was 70 deaths per 10,000 live births. In 1954, the beginning of our second twenty-five years, the rate was 5 per 10,000 live births—a remarkable improvement. If we concede, however, that 60 per cent of the 2,140* mothers who died of obstetric

*"In the 15th Century it was said: The presence of a physician helps a great deal. His role is to cure sometimes, to relieve often and to comfort always."

causes in 1954 could have been saved, 1,284 of these women would be alive today. This is a true challenge to our specialty and to our organization. We note too that in 1952, the latest year for which this information is available, the maternal death rate among the white population was 4.9 and among the non-white population 18.8. Had the white rate applied to the nonwhite mothers, 729 maternal lives would have been saved, over one-fourth of that year's maternal deaths.

There are many unsolved problems in gynecology also. A cure can rarely be claimed. Despite our increased knowledge of cancer, we do not know its cause and we speak not of cure but of survival. Our progress has been accomplished by the systematic collection and comparison of observations and by painstaking record of case histories. By use of this simple method of investigation we are gradually making headway in our fight against cancer.

"To relieve" is defined as to alleviate, or to free from pain, distress, anxiety, need, or fear. Descartes,²⁴ referring to the practice of medicine, wrote that science shall bear fruit principally because it will bring about the preservation of health, "which is without doubt the chief blessing and the foundation of all other blessings in this life." Most of our daily contacts with patients end in compromise. It is rarely possible to cure, but often possible to relieve.

"To comfort" is defined as to soothe when in grief; console; cheer; to make physically comfortable. It is comparatively easy to comfort any patient who may be cured or in whom the major complaint may be substantially relieved. Many patients, however, still present themselves to the specialist at such a late hour that they have no chance for a cure and possibly little chance for relief. It is in the care of these patients that we must be thoughtful. Should a patient be told that she cannot be cured? The answer to this question must be individualized but if the symptoms cannot be satisfactorily explained without telling the truth, the truth should be told. Otherwise, it is quite possible that the patient may develop a feeling that her physician does not realize the true extent of her illness. The truth in such a situation may result in a changed attitude, may relieve the worry caused by a feeling of indecision, and may permit many to spend their last days in peace.

A good working arrangement between the family physician and the specialist may contribute to the comfort of the patient. A sustained interest in the welfare of the patient on the part of the specialist may give a feeling of hope and comfort. On the other hand, if the specialist should turn the patient back to the family physician because the outlook is hopeless and indicates no further interest, this action may create great discouragement. The relationship between the patient and the physician is a true therapeutic factor and has an important bearing on the efficiency of any treatment, no matter how skillfully rendered.

Miller²⁵ writes, "Generally speaking, I do not consider the contemporary care for the advanced cancer patient to be as good as it might be. The specialist may know a great deal about the diagnosis and treatment of cancer but he is sometimes woefully weak in understanding and willingness to undertake ter-

*In 1954, there were 4,621,000 live births in the United States; there were 2,140 maternal deaths. This figure does not include deaths from nonobstetric causes.

minal care." He continues, "The satisfaction which comes to us at the end of a busy day can be enhanced immeasurably, if we have visited and done what we can for those who are about to die. . . . Today, as always, good medical care implies something more than personal service and advice. It includes a generous allotment of understanding—the art of our healing profession."

Program for the Coming Twenty-five Years.—

Twenty-five years ago the founders of this Association played an important role in the improvement of obstetric and gynecologic practice in this country. This was accomplished in part by individual and group study and research, and in part by a dedicated teaching program. The gain was remarkable and probably far exceeded the fondest hopes of those who worked so hard for that improvement. We must accept a real responsibility for a continuation of that dedicated program.

I should like to submit for your consideration a program for the coming twenty-five years. It is not greatly different from that set forth twenty-five years ago by those who saw a need for this organization.

First, we should continue our support of maternal death studies. These might well be broadened to include the study of perinatal mortality. Unnecessary deaths still occur from hemorrhage, toxemia, and infection. We must find solutions to the problems relating to heart disease and anesthesia which are now being reported as important killers. Serious attention should be given to the wide difference in nonwhite and white maternal mortality rates so that appropriate action may be taken. As we improve our results in these fields we shall have the experience to investigate other factors which adversely affect maternal and perinatal mortality and morbidity rates, such as nutrition, prematurity, and the abuse of operative procedures in obstetrics.

Second, consider the formation of a similar committee to study the needs in gynecology. The mortality from cancer alone can be greatly reduced by more widespread use of early diagnostic methods. The abuse of operative procedures in gynecology is in need of consideration.

Third, consider the over-all needs of the medical profession. More physicians are needed. Our premedical educational program must be revalued so that a proper balance between technical knowledge and a liberal education may be attained; in medicine the "whole man" must be trained. The medical curriculum must aim at the impossible; it must continue to advance the knowledge of new techniques and skills, and at the same time rediscover the individual and the community.

Fourth, consider the needs in obstetrics and gynecology. Encourage more "talented" medical students to enter this specialty. The needs in education and training constantly change as new fields develop in this and other specialties. At this time more training is needed in endocrinology and the physics of radiation, as well as a broader training in surgical gynecology, if this specialty is to attract more capable physicians.

Fifth, disseminate the knowledge we now possess. Techniques and treatment known to be good must be put to widespread practical use. To do this

we must plan a continuing educational program for all physicians who practice obstetrics and gynecology. Many physicians who are responsible for a large number of obstetrical patients are unable to go to medical centers for further training because they do not have adequate professional assistance in their communities. At the same time, knowledge of good treatment procedures must be made known to the public so that the best treatment may be demanded.

Sixth, it must not be forgotten that it will be impossible to cure all. Aristotle once said that the virtue of the citizen must be relative to the constitution of the state; so must be the relation between the physician and an organization such as this. In our deliberations here we tend to stress scientific progress and in our enthusiasm we may fail, on returning to private practice, to give those patients whom we are still unable to cure the individual consideration they deserve. We must not become so devoted to pure science that, when we cannot cure, we fail to offer the kindly warmth of relief and comfort. Without friendly concern we may appear to be callous. By using all of the scientific knowledge in our possession we may be able to cure; lacking that capacity, let us not forget the great virtue of relief and comfort.

*A merry heart doeth good like a medicine:
but a broken spirit drieth the bones.*

—Proverbs 17:22

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EDUCATION OF THE OBSTETRICIAN-GYNECOLOGIST*

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WE ARE a motley crew, you and I. Some of us are obstetricians, some are gynecologists, and some are both. A few of us are infertility experts almost exclusively, and a number of us are really female endocrinologists. Others of us emphasize the surgical aspects of our specialty while a few of us scarcely touch the knife. Some of us are cancer specialists and a few of us are pathologists. We have arrived at our respective accomplishments by many and devious routes; we are the products of all manner of different training programs. Whether we should be a more homogeneous lot I am not prepared to say, but because of our varied character there is little wonder that there is so much confusion regarding the desirable training program for qualification as an obstetrician-gynecologist.

There are many, both within our ranks and without, who believe that the combination of obstetrics and gynecology is illogical and impractical. They point out that if one is to be well qualified in gynecology one should have a considerable surgical background. Such a man should be prepared to deal with a large variety of bowel and urological conditions as well as with the gamut of genital lesions. On the other hand if one is to be a top-flight obstetrician he must have spent a good deal more than a year or two dealing with the many obstetrical complications. The critics of combined obstetrics and gynecology believe that adequate bilateral training, to the extent mentioned, is well-nigh impossible. They also point out that from the practice point of view the unpredictability of obstetrics frequently interferes with surgical efficiency, particularly if an operating room schedule is to be met, as is usually the case.

Those who believe that obstetrics and gynecology should remain wedded maintain that the problems of the reproductive function cannot be artificially divided if the best of medical care is to be accorded our women. They feel that those who are brought up exclusively in one of the disciplines often fail to appreciate the implications of the other, and thus do not see the picture whole. Whichever point of view one has, there is no doubt whatever that many problems exist in providing an adequate education in both branches of the specialty in a reasonable length of time. Great problems are also posed by the dearth of facilities for adequate education in both fields, particularly under one roof, for the large number of men who seek to qualify themselves as obstetrician-gynecologists. Despite these perplexities the majority of the leaders in our specialty appear to favor a combined program of education, as

*Address of the Guest Speaker, presented at the Twenty-third Annual Meeting of the Central Association of Obstetricians and Gynecologists, Columbus, Ohio, Oct. 6, 7, and 8, 1955.

I shall show later. There is less concern as to whether the graduates of these programs later choose to limit their practices to obstetrics, or to gynecology, or to do both.

The character of the resident training programs, whether stimulating and rewarding in clinical opportunity or not, has an important bearing upon the attractiveness of our specialty to students, interns, and residents and, in addition, is of great interest to all of us because the quality of future obstetrics and gynecology in America depends largely upon their content.

I should like to give you some of the high lights of an investigation of resident training programs in the United States which was carried out during the last year by a subcommittee (of a committee appointed by the American Gynecological Society to investigate factors involved in the attraction of talented men to the specialty of obstetrics-gynecology) consisting of Drs. Conrad Collins, Robert Kimbrough, Charles McLennan, William Mengert, William Dieckmann, and myself. I feel that this information is of interest and may be of value to all of us because it gives us a frame of reference and reflects present thought and arrangements. I propose then to comment upon some of the features discussed and to add my own views. Many of you have received a copy of a report on the information obtained during the investigation but others of you have not.

The investigation was carried out by means of a questionnaire. Queried were all 71 active four-year medical schools in the United States, and 42 large hospitals not directly affiliated with medical schools. Replies were received from 64 of the former and 34 of the latter.

With regard to internships, the majority, in both university and non-university hospitals favored a rotating internship, and indeed a few states require an internship of this character. In a dozen or more instances other internships were regarded as acceptable, such as internships in medicine, pathology, surgery, or straight obstetrics and gynecology. In 5 instances a surgical internship was reported as required. Only 4 indicated that they required a straight internship in obstetrics and gynecology. Nine indicated that "any good internship" was acceptable. The breakdown into university and non-university services is shown in Table I. From this information I gathered that there is no great concern over internships because the first year of assistant residency is depended upon to accomplish the kind of orientation and experience in the specialty which is ordinarily expected from an internship. Opinion appeared to be about equally divided as to whether the abolition of the straight internship in obstetrics-gynecology would prove a detriment to the ability to attract residents in hospitals where straight internships existed on other services.

TABLE I. INTERNSHIPS

| | UNIVERSITY | NON-UNIVERSITY | TOTAL |
|--------------------------------|------------|----------------|-------|
| Rotating | 52 | 32 | 84 |
| Straight obstetrics-gynecology | 12 | 5 | 17 |
| Straight surgery | 5 | 2 | 7 |
| Any good internship | 9 | 0 | 9 |

The length of the resident training program was three years or more in all of the university clinics responding, and in all except 4 of the non-university hospitals (Table II). Whether this tenure evolved because it was considered most desirable or because of the requirements of the American Board of Obstetrics and Gynecology is not entirely clear. In 22 of the university and 7 of the non-university services, however, a four-year program was re-

ported, and in 8 others fifth or sixth years were offered or required. In 16 additional instances the respondents indicated that they desired or had plans for a four-year program to replace their present three-year course. Among the universities there were two outstanding examples of separate departments, offering an integrated program in which the residents are trained predominantly in obstetrics or in gynecology, but presumably receive an adequate training in the related discipline as well (Johns Hopkins and Harvard). Most of those who have a program of more than four years indicated that the additional years were designed especially to give added opportunities to men who might wish to pursue an academic career. In only 4 instances (all non-university) were programs devoted to obstetrics or gynecology alone reported.

TABLE II. LENGTH OF RESIDENCY PROGRAM

| | UNIVERSITY | NON-UNIVERSITY | TOTAL |
|--|------------|----------------|-------|
| Two years or less | 0 | 4 | 4 |
| Three years | 36 | 21 | 57 |
| Three and one-half years | 2 | 2 | 4 |
| Four years | 22 | 7 | 29 |
| More than four years } Plus special additions } | 6 | 2 | 8 |

There was a considerable difference of opinion as to whether the structure of the program should be a parallel or a pyramidal one (Table III). The majority favored the parallel system. The pyramidal program is criticized by many, especially residents, who like to feel that if they are accepted at all their entire training will be guaranteed, at least to the extent of Board requirements. While this may prove no difficulty where large services are available, it poses great problems in the smaller centers. Certainly a service which has been watered down simply to satisfy on paper a Board requirement is not an adequate solution.

TABLE III. STRUCTURE OF PROGRAM

| | UNIVERSITY | NON-UNIVERSITY | TOTAL |
|-----------|------------|----------------|-------|
| Pyramidal | 26 | 7 | 33 |
| Parallel | 37 | 25 | 62 |

An effort was made to obtain information regarding the desirability and/or essentiality of (1) certain special features (such as rounds, clinical pathological conferences, seminars, journal clubs, radiological rounds, tumor conferences, etc.) and (2) exposure to related disciplines (such as pathology, surgery, psychiatry, endocrinology, clinical laboratory services, etc.). These portions of the questionnaire were not answered in sufficient detail to permit a very revealing analysis though it seems to your essayist that such considerations are of the greatest moment. The information obtained is presented in Tables IV and V. Most services reported a period of time on pathology (83) and a weekly pathology conference (75). A number of those who do not have such features expressed the wish that they did have. Rounds by a senior person, daily, or several times a week are conducted at most institutions (82), and most of them (74) hold special conferences of one sort or another, like journal club, tumor board, basic science lectures, etc., but there was no very frequent or consistent pattern revealed by the reports.

With regard to research: In 9 university clinics a period of time on research is required of all residents, or a thesis is required. In many others opportunities are offered or encouraged. Some seem to feel that more research should be demanded, and others that research has no part in a resident's training. Statements regarding the character of research opportunities were

too varied to permit tabulation. The two terms "clinical" and "laboratories available" were used most frequently. Nine clinics reported "no opportunities."

TABLE IV. SPECIAL FEATURES (1)

| | UNIVERSITY | NON-UNIVERSITY | TOTAL | COMMENT |
|---------------|------------|----------------|-------|--|
| Pathology | 56 | 27 | 83 | Usually both general and gynecological |
| Surgery | 19 | 7 | 26 | Actual service—13 |
| Urology | 18 | 4 | 22 | Actual service—11 |
| Endocrinology | 14 | 3 | 17 | Actual service—6 |
| Psychiatry | 7 | 0 | 7 | Actual service—1 |

TABLE V. SPECIAL FEATURES (2)

| | UNIVERSITY | NON-UNIVERSITY | TOTAL | COMMENT |
|---------------------|------------|----------------|-------|---|
| Clinical laboratory | 5 | 0 | 5 | Actual service—3 |
| Biochemistry | 3 | 0 | 3 | |
| Pathology seminar | 48 | 27 | 75 | Usually once a week |
| Rounds | 54 | 28 | 82 | Usually 2 to 3 times a week |
| Special | 49 | 25 | 74 | e.g., Journal club, tumor board, radiology, basic sciences, anesthesia—no pattern |

In almost all of the university, and in many of the other hospitals, some teaching is carried out by the residents—of nurses, students, or interns—on wards, in operating and delivery rooms, in conferences, or as lectures.

One of the most pertinent questions regarding resident training programs would seem to be the amount of clinical material available for study and operative experience. However, no consistent picture was found, and it may well be that one cannot compress the value of a program of this type into mere figures even though we all realize that a resident must have a "reasonable" amount of practical experience. Table VI contains the information regarding beds (only 56 university clinics reported the exact number of beds). One university clinic has as many as 210 and one as few as 35 beds. Only a few reported less than 50 or more than 100 clinic beds.

TABLE VI. BEDS

| | UNIVERSITY (56) | NON-UNIVERSITY (26) |
|----------------------|-----------------|---------------------|
| <i>Obstetrics.</i> — | | |
| Clinic | 50 (65%) | 24.3 (29.5%) |
| Private | 26 | 47.6 |
| Total | 76 | 71.9 |
| <i>Gynecology.</i> — | | |
| Clinic | 31.6 (63%) | 18.5 (35.5%) |
| Private | 18.4+ | 33.5+ |
| Total | 50 + | 52 + |
| All clinic beds | 81.6 | 42.8 |

Since the actual number of beds available may be of importance only in relation to the number of residents and the length of their training, an attempt was made to develop a formula which would take all three of the variables into consideration and be of some value as a measure of adequacy. Information from 55 university hospitals and 26 non-university affiliated institutions was available for this calculation (Table VII).

The resultant figures varied markedly and inconsistently all over the country. The highest was 210 and the lowest was 12. Often gynecological beds were indicated as varying in number. Often it was mentioned that beds in affiliated hospitals were available for some functions. Variability in number of residents and years of training was also indicated occasionally. The figures used were the minimums mentioned. Obviously no conclusions can be drawn. These figures are meaningless at this time but may be of value in the future since all three variables must be considered in an evaluation of this type.

TABLE VII. CORRELATION: BEDS, RESIDENTS, TENURE. FORMULA: $\frac{B \times Y}{R}$

| | UNIVERSITY | NON-UNIVERSITY | ALL |
|---------|------------|----------------|------|
| Average | 48.5 | 55.2 | 50.7 |
| Median | 42 | 50 | |

Only a few hospitals require of their residents a specific number of operative or other procedures, or experience in the management of a selected list of complications. Most of the respondents replied that their residents managed or operated upon "all or almost all of the clinic patients." A few referred to "the gamut" of obstetrical and gynecological procedures. Many remarked that the residents had ample operative opportunity.

Suggestions for improvements in programs were extremely varied. Those mentioned most often were:

| | |
|-----------------------------|----|
| Increase program to 4 years | 16 |
| More research | 12 |
| More pathology | 11 |
| Exposure to surgery | 13 |
| Exposure to urology | 7 |

Also mentioned were "more patients," "full-time teachers," "more money," "office gynecology," more "basic science." Deplored were "the draft," "early marriage," "lack of space," etc.

The results of this questionnaire study leave us far from satisfied. There appear to be certain reasonably common features, however, which characterize the programs of training in obstetrics and gynecology today in our university hospitals and in a considerable number of other large hospitals. The most common features are: a previous rotating internship; usually a three- but fairly often a four-year residency, arranged in parallel fashion; a combined obstetrical-gynecological service; six months of mixed general and gynecological pathology and a weekly clinical-pathological conference; frequent (usually daily) rounds by a senior staff member; and less frequent special features such as journal clubs, special basic science lectures, radiological conferences, etc.); indifferent research opportunities; some teaching duties; about 50 clinic obstetrical and 31 clinic gynecological beds; infrequent and inadequate opportunities in related fields such as surgery, urology, and psychiatry. This type of program represents the best of the picture; this is what is offered in our university clinics and a sizable sample of the larger non-university hospitals. We are all aware, however, of the very great number of men who are receiving their training on smaller and often less well-organized services all over the country, frequently, of necessity repeating a one-year residency three times in order to meet American Board requirements. We are also well aware of the large number of men who receive a portion of their specialty education through the medium of the preceptorship, often an unsatisfactory method

because of the indifference and lack of preparation of the preceptor. Incidentally, the Board is well aware of these problems and is striving hard to solve them.

At this point it might be of interest to look briefly at the over-all picture of resident training programs obtained from information presented in the Sept. 25, 1954, issue of the *Journal of the American Medical Association* with reference to all of the approved residencies in obstetrics and gynecology offered in the United States (Table VIII). Of special note is the fact that almost half of the programs offered are of less than three years' duration, thus necessitating additional training elsewhere for the residents serving in these institutions. Also of interest is the small number of straight gynecological residencies approved throughout the country, only 14; and the infinitesimal number of three-year programs in this category, only 2. If this be a true representation there is little wonder that residents have such a difficult time obtaining an adequate volume of gynecological experience. Also it can be observed that, at least on paper, three-year combined services are by all odds the most popular. While obviously there is no one road to wisdom and learning, this picture of what is offered for the education of the obstetrician-gynecologist today leaves much to be desired.

TABLE VIII. APPROVED RESIDENCIES AND FELLOWSHIPS IN OBSTETRICS AND GYNECOLOGY, 1954.*
TOTAL AVAILABLE, 2,003

| PROGRAMS | ONE-YEAR | TWO-YEAR | THREE-YEAR | TOTAL |
|---------------------|----------|----------|------------|-------|
| Straight obstetrics | 38 | 22 | 6 | 66 |
| Straight gynecology | 6 | 6 | 2 | 14 |
| Combined service | 55 | 91 | 224 | 370 |
| Total | 99 | 119 | 232 | 450 |

*J. A. M. A. 156: pp. 368-373, Sept. 25, 1954.

Comment

My effort has been to picture the principal features of resident training in obstetrics and gynecology as it exists in the United States today. What it should be is another question and certainly I do not presume to have the answer. I would like to discuss some of the features more fully, however. First of all, it seems to me that it would be very helpful if those who are charged with the responsibility of conducting resident education could agree upon the essentials, with the thought that all services could and would aim at providing them in their programs. Inevitably there would be variations dependent upon individual circumstances, of facilities, of men, of money, and of special interests, and this is probably as it should be. Should any plans be developed it would be of inestimable value and importance for our national societies and the American Board to be back of them.

The curricula of the medical schools today are becoming more and more crowded with the result that the amount of time allotted to the teaching of obstetrics and gynecology is shrinking. It has become impossible, as it has with most other disciplines, to attempt to teach all of the facts. We have been reduced to hardly enough time for the relatively few basic considerations. Possibly this is understandable since, after all, obstetrics and gynecology have become more and more of a specialty and less and less a part of general practice. Our effort must be to give to students a bird's-eye view of the important

anatomical and physiological facts and the principal abnormal conditions, and to reveal the most important sources of information. We can hope to stimulate and inspire but we cannot expect to equip our medical students with enough of the detailed knowledge of obstetrics and gynecology to permit them to practice the specialty without further training.

With regard to internship I believe that the trend revealed in our study is reasonable and sound, viz., a rotating (or mixed) internship is preferable, but probably any good internship should be acceptable. As a matter of fact, I doubt if the straight internship in obstetrics and gynecology is quite as inadequate as it appears to be regarded at this time. Possibly there will be problems in attracting a fair share of superior interns to go into obstetrics and gynecology in those institutions in which straight internships in medicine, surgery, pediatrics, etc., exist, but none in obstetrics and gynecology. Whatever is formally labelled "internship," it would appear that the first year of a residency program should and does act as an internship in obstetrics and gynecology. I believe that this is appropriate since it is manifestly impossible to provide very much obstetrical and gynecological experience in a rotating internship—and none at all in straight internships in other fields.

Like most others I feel that education in obstetrics and/or gynecology is best provided through the medium of a combined service, though it is evident that this entails numerous difficult problems in the provision of experience in closely related fields like surgery and urology. The problem is one not only of facilities but also of time. If it were agreed, and I believe that it should be, that exposure to a selected experience in surgery, urology, psychiatry, endocrinology, pathology, and clinical laboratory is desirable in the education of the obstetrician-gynecologist, then it seems obvious that the length of the training program must be extended to a minimum of four years. Possibly even more time would be desirable. While most programs are currently three-year ones, many seem to feel the need of more time. Moreover, I believe that the three-year program rather than a longer one has come about largely through force of circumstances rather than deliberate planning. The determining circumstances have been the resident's economic plight, the unavailability of experience in related fields (or lack of planning for it), an insufficiency of suitable teaching material, and the requirements of the American Board of Obstetrics and Gynecology, which are largely a distillate of minimal desirable requirements, available programs, and economics.

Besides exposure to three years of clinical obstetrics and clinical gynecology in equal proportions in positions of gradually increasing responsibility, additional experience in the disciplines enumerated above would seem to me to be a necessity if our aim is to be for the optimum.

Pathology, both general and special, has been appreciated in the past and should continue to be in the future. There is a peculiarly intimate association between clinical gynecology and its basic pathology. To study gynecological pathology is to gain a concept of gynecological conditions which cannot be gained in any other way. Many services include six months of pathology and a weekly clinical-pathological conference. This seems satisfactory to me.

Enough surgery to be familiar with general surgical principles and to be capable of dealing with bowel complications should certainly be acquired during the course of training. The gynecologist should know how to recognize and manage, both medically and surgically, intestinal obstruction, gastric dilatation, and adynamic ileus; he should be able to resect bowel and perform colostomy. Few services have been able to include adequate training of this type and I do not know how the deficiency should be remedied. If it were possible, active participation on a surgical service during which opportunities of the sort mentioned were offered would be the best. This has not usually been possible, however, and in my opinion is not likely to be in the future. Dog surgery might furnish a reasonable substitute for the technical aspects. Otherwise the concept, on all services, of having the residents follow through in the examination and care of individual patients, including those referred to other services (e.g., surgery) and participate in treatment procedures there might provide an answer.

Exposure to certain urological procedures and examinations would be highly advantageous. This too has received short shrift in the past in most institutions. I believe that the desired end could be accomplished reasonably easily by means of scheduled attendance at cystoscopic clinics, and possibly by gynecological and urological residents sharing in the care and treatment of the overlapping conditions, like fistula, incontinence, etc.

In the case of psychiatry and clinical laboratory it seems that in both instances the exposure would have to be accomplished by dealing with the particular problems as they occurred in gynecological cases, with close collaboration between the responsible resident and the appropriate expert consultant. The importance of acquiring some familiarity with the recognition and management of psychiatric components of gynecological diseases needs no justification. Also, I think it quite evident that up to the present such problems have not received the attention they deserve. It is my belief that thought and planning should be directed toward remedying this deficiency in every obstetrical and gynecological resident program.

With regard to clinical laboratory, I have in mind such problems as fluid and electrolyte balance, the techniques and significance of hormone determinations, the bacteriology of the female genital tract, etc. In addition to a collaborative effort related to individual patients it would seem that a series of seminars or lectures on pertinent subjects of the sort mentioned would add to the effectiveness of the resident's education.

Since so many gynecological conditions are intimately tied up with aberrations of ductless gland function, a thorough appreciation of endocrinological physiology should be in the possession of every graduating obstetrical and gynecological resident. I believe that sufficient opportunity could be presented by having all residents spend a reasonable period of time in an outpatient clinic devoted to such problems, possibly in conjunction with the infertility clinic. If possible an endocrinologist should be in attendance as well as a gynecologist.

The matter of research opportunities is certainly a controversial one. In my opinion a period of time on research should be included in the training period, if not for all, then for those who show aptitude for or who express interest in an academic career. I do not know where it should come, but suspect that it would be best near the end, i.e., after three years, or perhaps even after five years. But, even before this time every resident should be required to participate in some clinical research investigation because it would give him some familiarity with the literature of the specialty, it would teach him how to marshall facts and write them up, and it would give him the experience of presenting them to the staff.

Other special features which are currently included in many resident training programs, which I regard as a "must" are: (1) a weekly staff conference or grand rounds, (2) daily or almost daily ward rounds with a senior staff member, (3) a weekly seminar on special subjects (e.g., radiological problems, both therapeutic and diagnostic, the Rh problem, virus diseases in pregnancy, toxemia, etc.), (4) a journal club, and (5) a weekly chart review. None of these require discussion, but all I believe are essential.

Two final problems of different nature invite some comment. The first has to do with the amount of clinical material available per resident. At the present time there is marked variation in this respect as was pointed out earlier. Whether a minimum should be established I do not know. As a matter of fact there are evils associated with too many patients as well as with too few. The most common problem at the present, however, is the diminishing number of clinic patients. More and more have acquired private patient status by virtue of hospitalization and medical care insurance. While this is good socially, it has diminished residents' opportunities in all of the surgical specialties particularly. I believe that the problem can be solved but it will require some revision of thinking and policy. First of all, it is quite possible to conduct a great deal of valuable resident education with private patients as subjects; a great deal has been carried out in the past, and more is possible in the future, with the sympathetic cooperation of private practitioners and a better understanding by patients of the resident's role in their care. This resolves itself into a selling job—we have to sell the idea of teamwork. Many patients misunderstand, and when they do I think it well worth the time and effort to stop and explain. I see no reason why residents should not be guided through many procedures carried out on private patients. Naturally the patient's doctor remains the responsible member of the team. Perhaps these men in training should be regarded and called "my assistants" rather than "the residents." This would at least exemplify the type of relationship and the place of the resident's responsibility that we must try to sell. Second, a change in the attitude of organized medicine and of insurance companies toward the treatment of patients with some types of insurance by residents would be of great help in amplifying opportunities. Should it not be possible for residents to treat patients with hospitalization insurance only, or those with small medical care provisions? Funds could be collected toward a house

staff fund, or research without interfering seriously in the rights and prerogatives of private practitioners. Such changes in viewpoint must be sought and can be accomplished I think if we as a specialty get behind them.

The last point for discussion revolves around the average resident's economic plight. If we are to promote long periods of training we must make it economically possible. Many residents are married and have children—they must live. I hear my former chiefs snort at the idea of even accepting married men as residents. Certainly most of us were brought up in the days when residents were provided with little more than subsistence and the opportunity to obtain training in the specialty. Well, times have changed and we must face it. Medical training is long enough without four years of specialty training added on. I believe that in some way increasing financial assistance must be provided as our residents progress through the steps of training. How? I do not know. Possible steps are: (1) make a concerted effort to impress upon hospital and university administrators the vital necessity of providing increased financial remuneration for residents; (2) arrange with insurance companies which provide medical care insurance for the allowed doctor's fee which would ordinarily be paid to the practitioner to go toward a resident's fund in cases in which the patient is accepted as a "clinic" case.

In conclusion, may I say that it is my belief that resident training programs have improved greatly in this country in the last twenty-five years, but that there is still much to be accomplished and new problems must be met? With some thought on the part of all of us I consider it entirely possible that agreement can be reached regarding many desirable features and minimum standards. This should be the first step. The second step is that of implementation, and while difficult I do not believe that the problem is insurmountable.

CARDIAC OUTPUT DURING LABOR*†

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THE basic outline of changes in cardiac output in pregnancy has been well documented during the past generation. It is now generally agreed that the cardiac output rises rapidly from the end of the first trimester and increases progressively until some time in the eighth lunar month, when it attains a level approximately 30 to 35 per cent greater than the cardiac output in nonpregnancy. There has been described an "immediate postpartum rise" which is again followed by a gradual drop after the first week post partum.¹

The information which has been made available to date concerning cardiac output has been most useful in promoting an understanding of the impact of pregnancy upon the circulatory system in broad general terms. The previously available information, however, deals sketchily, if at all, with determinations of cardiac output performed under conditions of actual labor.

A rise in cardiac output may indicate response to such diverse stimuli as: (1) tissue demand for oxygen, (2) the need for redistribution of the circulating volume, (3) postural changes, or (4) the patient's anxiety or pain. Since all the factors mentioned are involved in the dynamic process of labor, it should be anticipated that the dramatic changes accompanying parturition might well have equally dramatic implications for cardiac performance.

A study of the cardiovascular implications of these significant events forms the subject of the present report. The cardiac output determinations of pregnant patients reported up to the present time have suffered from their nonrepeatability. Some methods involve cardiac catheterization, a valuable technique which nevertheless is not carried out or repeated lightly. Methods involving the use of Evans blue are limited by the fact that each determination requires an additional injection of the blue dye which will produce unpleasant and prolonged skin staining if large enough cumulative dosage is attained. Both of these methods have the further disadvantage that a single determination cannot be finished within a matter of seconds and then repeated almost immediately.

Using a different method than has been employed previously in pregnancy, the output determinations reported in this study were carried out not trimester by trimester, or even week by week, but sequentially, almost second by second in some cases. This has given an opportunity for study of the cardio-

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vascular changes within such brief but important phenomena as isolated uterine contractions, and the immediate effects of medication or placental separation.

Methods

A. *The Rationale.*—

The studies reported here make use of the so-called "blood pressure method" or "pulse pressure method" for the estimation of cardiac output. In essence, the method utilizes the old observation that there is a direct relationship between pulse pressure (as measured in millimeters of mercury) and cardiac stroke output (as measured in cubic centimeters). Since its proposal by Erlanger and Hooker,² in 1904, the method has attracted both advocates²⁻⁴ and critics.^{5, 6} An early attempt was made by Slemons and Goldsborough³ to use pulse pressure in estimating the degree to which cardiac output was raised during pregnancy, but the techniques available were not sufficiently accurate to yield significant results.

In more recent years, the method has been reappraised by more effective techniques of study. Cadaver studies of anatomic variations in aortic characteristics, cadaver simulation and measurement of systolic pulsations, statistical analysis of large numbers of clinical observations, accurate devices for recording arterial pressures, and the development of good and reasonably feasible comparative methods of determining cardiac output have all contributed to a better understanding both of the limitations and of the possibilities of the pulse pressure method.^{7, 8} Attempts have been made to bring the method into a wider sphere of clinical usefulness by the incorporation of correction factors based variously on the age of the patient, body surface, or the known increasing arterial distensibility at higher pressures.

The advantage of frequent repeatability over long periods of time makes the method most attractive for the study of obstetric conditions. Recent work with young, healthy obstetric subjects, based on conversion factors developed by Remington and associates,⁷ has indicated a gratifyingly good correlation between output determinations by the dye method and those done by the blood pressure method.⁹ The correlation remains equally good regardless of whether the patients are pregnant but not in labor, actually in labor, or post partum. Repeated correlation tests under differing conditions continued to give satisfactory results.

It may thus readily be appreciated that, given a direct and continuous recording of the arterial blood pressure, it is possible to estimate cardiac output performance repeatedly and at very short intervals over a relatively extended period of time. This advantage of frequent repeatability—over 350 output estimations have been made during the course of a single labor—is felt to be sufficient to warrant investigations carried out by this method in spite of the fact that no claim is made that the pulse pressure method is as accurate as the dye dilution method in any absolute sense. It is believed, however, that changes in the output as indicated by the pulse pressure method within the same individual and at the same testing period are most certainly of significance, and that the *percentage* changes are reasonably accurate. Furthermore, the measurement of alterations within a single individual (using the individual as his own control) offers some advantages over the attempted interpretation of results obtained by single determinations in a larger number of individuals. The limitations of drawing conclusions on the basis of single tests become alarmingly great in trying to measure biologic phenomena which have so large a variation of "normal" values as obtains in cardiac output. The "normal range," even when partially corrected by reduction in all pa-

tients to a value per square meter of body surface, is still so large that it is impossible to give for any event *the* normal value, or *the* usual value, but only a *range of values*. Oftentimes the range of values is so extensive that unless very large numbers of patients are studied in each group, the evaluation of subtle changes by the single-determination-in-a-group method becomes practically impossible. For this reason, single values have been omitted as much as possible in this study, and percentage change values have been emphasized.

TABLE I. THE 47 PATIENTS STUDIED

| NUMBER AND INITIALS | AGE | HEIGHT (CM.) | WEIGHT (KG.) | SURFACE (M ²) | CONDITION WHEN STARTED |
|---------------------|-----|--------------|--------------|---------------------------|---|
| 1 M. C. | 18 | --- | --- | --- | 45 minutes post partum |
| 2 J. J. | 29 | 188 | 84.5 | 2.09 | Term; early labor |
| 3 M. J. | 22 | 165 | 70.0 | 1.78 | Term; labor |
| 4 M. S. | 20 | 165 | 68.6 | 1.76 | Term; early labor |
| 5 J. R. | 21 | 167 | 68.4 | 1.77 | 39 weeks; early labor |
| 6 H. A. | 32 | 170 | 77.7 | 1.88 | 24 hours post partum |
| 7 M. Ra. | 35 | 164 | 74.0 | 1.82 | 29 weeks; not in labor |
| 8 D. R. | 22 | 157 | 52.0 | 1.51 | 36 hours post partum |
| 9 M. R. | 21 | 168 | 72.0 | 1.82 | 2½ hours post partum |
| 10 Y. S. | 18 | 152 | 56.5 | 1.51 | Term; not in labor |
| 11 M. Ry. | 22 | 161 | 66.0 | 1.69 | Labor, delivery, post partum |
| 12 T. H. | 20 | 153 | 67.0 | 1.64 | 39 weeks; labor |
| 13 L. J. | 26 | 170 | 86.3 | 1.97 | 44 weeks; section, post partum |
| 14 R. W. | 31 | 160 | 67.8 | 1.71 | 38 weeks; early labor; section, post partum |
| 15 G. W. | 35 | 159 | 65.1 | 1.64 | 38 weeks; not in labor |
| 16 P. S. | 25 | 160 | 71.0 | 1.74 | 41 weeks; labor, delivery, post partum |
| 17 H. S. | 20 | 167 | 55.4 | 1.63 | 35 weeks; not in labor |
| 18 E. M. H. | 19 | --- | --- | --- | 41 weeks; labor, delivery, post partum |
| 19 M. Sa. | 18 | 153 | 46.1 | 1.40 | 4 hours post partum |
| 20 M. G. | 25 | 163 | 67.0 | 1.71 | Term; labor |
| 21 R. A. | 22 | 163 | 60.0 | 1.64 | 20 weeks; not in labor |
| 22 B. A. | 21 | 171 | 56.9 | 1.66 | ½ hour post partum |
| 23 P. D. | 16 | 166 | 66.0 | 1.74 | 4 hours post partum |
| 24 Z. M. | 19 | 170 | 75.5 | 1.86 | 38 weeks; active labor |
| 25 C. P. | 20 | 153 | 66.2 | 1.64 | 38 weeks; labor |
| 26 W. H. | 22 | 160 | 66.4 | 1.70 | 3 hours post partum |
| 27 M. T. | 32 | 161 | 60.0 | 1.63 | 42 weeks; not in labor |
| 28 B. A. | 16 | 150 | 57.1 | 1.50 | 1½ hours post partum |
| 29 T. H. | 38 | 170 | 81.0 | 1.92 | 7 hours post partum |
| 30 D. T. | 15 | 162 | 62.0 | 1.65 | 39 weeks; active labor |
| 31 J. L. | 21 | 160 | 65.0 | 1.68 | 36 hours post partum |
| 32 M. H. | 21 | 153 | 43.0 | 1.33 | 48 hours post partum |
| 33 M. K. | 26 | 157 | 61.4 | 1.62 | 58 hours post partum |
| 34 M. F. | 22 | 164 | 60.0 | 1.65 | 9 hours post partum |
| 35 J. B. | 19 | 165 | 61.2 | 1.68 | 3 hours post partum |
| 36 T. D. | 25 | 158 | 47.4 | 1.46 | 4 hours post partum |
| 37 C. D. | 18 | 172 | 54.2 | 1.64 | 6 hours post partum |
| 38 E. H. | 20 | 160 | 62.7 | 1.64 | Term; active labor |
| 39 J. H. | 19 | 163 | 66.1 | 1.70 | Term; labor |
| 40 B. M. | 19 | 161 | 70.0 | 1.74 | Term; labor |
| 41 L. M. | 28 | 156 | 80.9 | 1.80 | 38 weeks; elective section, post partum |
| 42 B. S. | 20 | 163 | 82.7 | 1.87 | 38 weeks; elective section, post partum |
| 43 A. G. | 24 | 165 | 81.3 | 1.89 | Term; active labor |
| 44 J. Ra. | 20 | 171 | 72.2 | 1.83 | Term; long labor, section post partum |
| 45 L. Ja. | 28 | 157 | 58.1 | 1.58 | Term; labor, delivery, post partum |
| 46 L. M. | 26 | 165 | 70.0 | 1.78 | 36 weeks; not in labor |
| 47 B. F. | 22 | 163 | 68.6 | 1.75 | Term; labor |

B. The Procedure.—

The 47 patients studied in this series were predominantly young, healthy patients at term who were either approaching labor, in labor, or post partum. It may be seen from Table I that the average age of these patients was 22.9 years. Eighty per cent were 26 years of age or under, and only one was over 35. None showed clinical evidence of edema or significant hypertension. Most of the patients who were in labor had received mild to moderate analgesic medication, although some had received none. With few exceptions the patients who were studied at delivery had been given some form of conduction analgesia.



Fig. 1.—The equipment. A, Electromanometer, which is connected through a saline-filled lead tube to the brachial artery needle. B, Power unit. C, Recorder. D, Tokodynamometer. E, Sample collector used in performing correlative dye-method output determinations.

The actual procedure was carried out by introducing an 18-gauge Courmand-type needle into the brachial artery. The arterial needle was connected to a lead tube approximately 18 inches long, which was filled with a heparinized saline solution. The lead tube was attached to a Sanborn electromanometer. Continuous records of arterial pressure were made with a Sanborn Visocardiette (Fig. 1).

The timing of significant events occurring during labor or delivery was meticulously recorded on the continuous tape in order that cardiac output changes induced by any of the obstetric phenomena under observation might be well correlated. In those patients who had output determinations done during labor, a multiple lead, externally recording tokodynamometer* was used to give visual evidence as well as a printed record of the state of uterine contractility. It thus became possible to correlate the tokodynamometer record with cardiac output estimations at very frequent intervals. Under most circumstances, output estimations were done every six seconds. As a control, the blood pressure determinations were checked simultaneously by the dye method¹⁰ in nearly half the patients.

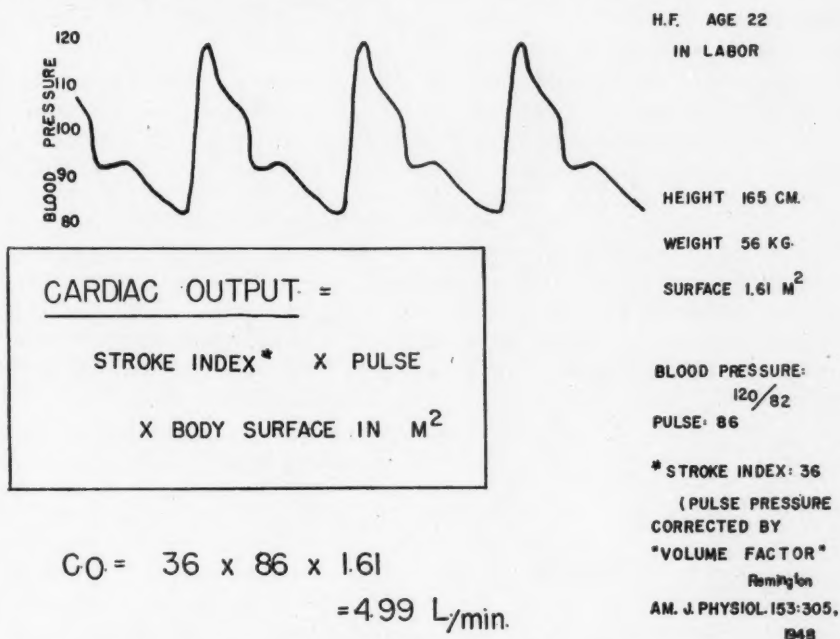


Fig. 2.—The determination of cardiac output from the arterial blood pressure.

C. Calculations.—

Remington and his associates⁷ derived a series of factors for the prediction of stroke index designed to indicate a smaller and thus more accurate volume equivalent at higher blood pressure levels. After applying the Remington "volume factors" to both the arterial systolic and diastolic pressures, the stroke index (cubic centimeters of heart output per beat per square meter of body surface) is represented as the difference between the systolic and diastolic volume factors. Having determined the stroke index, it is a simple matter to complete the estimation of cardiac output, which is calculated as follows:

$$\text{Cardiac output} = (\text{systolic volume factor} - \text{diastolic volume factor}) \times \text{heart rate} \times \text{square meters of body surface.}$$

An example is shown in Fig. 2. In this case, the blood pressure was 120/82. The Remington "volume factors" for pressures of 120 and 82 are

*Manufactured by Statham Laboratories, Inc., and donated by Wyeth Laboratories, Inc., Philadelphia, Pa.

100 and 64, respectively. The difference between the volume factors, 36, represents the *stroke index*, or the number of cubic centimeters of blood put out by each systole per square meter of body surface. Multiplying the stroke index by the pulse rate (in this case 86) gives the *cardiac output index*, or the amount of blood put out by the heart each minute per square meter of body surface. If the *total cardiac output* is desired rather than the cardiac index, the index is multiplied in turn by the number of square meters of body surface, in this case 1.61, giving a cardiac output of 4.99 liters per minute.

It has been stated by some workers that the use of the cardiac index in pregnancy states is not valid, both because of the unique body shape of the pregnant patient and because part of the weight of the patient in pregnancy represents "dead space" in so far as the cardiac output is concerned. These criticisms warrant some examination.

In regard to the criticism that the unique body shape in pregnancy invalidates the use of standard surface tables, it may merely be pointed out that the original work correlating the dye method and the pulse pressure method in pregnancy, labor, and post partum⁹ included the use of the body surface calculations from a Du Bois table. All the methods previously offered for the calculation of cardiac output from blood pressure were carefully examined and tested. The Remington method, which includes the use of the cardiac index, gave the most satisfactory results by far. There was agreement within 25 per cent between the dye method and the pulse pressure methods in 27 out of 30 observations, a degree of correlation which compares not unfavorably with comparisons between other, more orthodox, methods of determining cardiac output.

The statement that the products of conception represent "avascular" tissue insofar as it applies to maternal cardiac output is perfectly true. It should be borne in mind, however, that the cardiac output is functioning in proportion to the metabolic needs of the entire body, including the metabolically tremendously active contents of the amniotic sac. Moreover, the degree of inaccuracy is probably small. For example, in a patient 170 mm. in height who weighs 60 kilograms in late pregnancy, the body surface, according to the standard Du Bois table, is approximately 1.69 square meters. If we assume that the pregnancy accounts for 5 kilograms of the patient's weight and recalculate body surface according to the new weight, the body surface drops to 1.63 M², a diminution of only 3.55 per cent from the original calculation. Thus, even if we assume for the moment that the pregnant patient's cardiac output functions according to her nonpregnant weight, the error is not a great one, particularly when one is measuring a biologic function where, in comparisons by two methods, a scatter of 25 per cent in the results is to be expected.¹⁰

The use of the cardiac index rather than the total cardiac output makes unnecessary the decision as to whether the output of the patient studied continuously during delivery and the early puerperium must be calculated according to a given surface area up to the moment of delivery and according to a smaller surface area immediately post partum. In practice, however, the percentage error is probably a small one.

Finally, it should be borne in mind that the primary purpose of this work is to study the changes within each patient under the influence of various phenomena of parturition. In this way, since the patient serves as her own control, and since any error in calculating output by the use of body surface will be included in each determination, the final determination of *percentage change* from one observation to another will not be affected.

For these reasons, and because the cardiac index offers an approach to the standardization of results, the cardiac index is used in reporting all the data from this study. In most cases, as may be seen in Table I, the calculated body surface varied over a rather narrow range. In actual practice, the arterial pressures taken were the averages of one or more series of four consecutive heartbeats.

Results

A. Normal Uterine Contractions.—

Changes in cardiac output during an effective uterine contraction are predictable in character and surprisingly large in amount. Of the patients studied during active labor, all showed a consistent increase in output during uterine contractions. This increase averaged 30.9 per cent above the baseline cardiac output level for the precontraction interval (Table II and Fig. 3).

TABLE II. CHANGES IN CARDIAC OUTPUT AT THE HEIGHT OF UTERINE CONTRACTIONS IN ACTIVE LABOR

| PATIENT | CARDIAC OUTPUT/M ² PRECONTRACTION | CARDIAC OUTPUT/M ² HEIGHT OF CONTRACTION | PERCENTAGE INCREASE |
|---------|---|--|------------------------|
| L. J. | 2.90 | 4.26 | 46.9 |
| D. T. | 2.93 | 4.39 | 49.8 |
| D. T. | 2.62 | 3.95 | 50.7 |
| M. J. | 2.99 | 3.94 | 31.8 |
| L. J. | 3.26 | 4.20 | 29.5 |
| L. J. | 3.91 | 5.00 | 27.9 |
| J. R. | 2.90 | 3.30 | 13.8 |
| L. G. | 3.71 | 4.21 | 13.5 |
| L. G. | 3.55 | 3.85 | 8.5 |
| L. G. | 3.38 | 3.76 | 11.2 |
| E. H. | 5.20 | 6.20 | 19.2 |
| E. H. | 4.31 | 5.33 | 23.7 |
| J. H. | 4.48 | 6.75 | 50.7 |
| J. H. | 4.30 | 5.78 | 29.8 |
| J. H. | 3.90 | 6.43 | 64.9 |
| B. M. | 3.83 | 5.05 | 31.9 |
| B. M. | 4.26 | 5.05 | 18.5 |
| M. R. | 2.90 | 4.28 | 47.6 |
| T. H. | 3.43 | 4.51 | 31.5 |
| T. H. | 3.70 | 4.30 | 16.2 |
| Average | 3.62 | 4.73 | 30.9 |

There may be seen in Fig. 4 a typical example of the correlation between a uterine contraction and predictable cardiac output changes. It will be noted that, with the early onset of a contraction as indicated by the tokodynamometric tracing, there is a steady, rapid rise in the indicated cardiac output. The output reaches a peak within 18 to 30 seconds (depending on the type of contraction), a peak which is usually maintained until there has been some lessening in the intensity of the uterine contraction. With the waning of the contraction, after a rapid initial drop for 12 to 18 seconds, there is a fairly consistent but small rise in cardiac output before the output level subsides to the truly "resting phase." The significance of this small secondary rise will receive comment later.

B. Ineffective Uterine Contractions.—

A number of patients were studied under conditions of ineffective labor. In these patients there was seen a rather marked contrast to the orderly cor-

relation between cardiac output and uterine tone observed in the effective type of contractions. Among the patients who had ineffective uterine contractions, the output response to a given contraction was neither predictable nor consistent, either in timing or in amount. Table III indicates the rather wide variation observed in changes in cardiac output in poor labor. The average increase in output during an ineffective contraction was 19.2 per cent, less than two-thirds the increase found in the effective contractions.

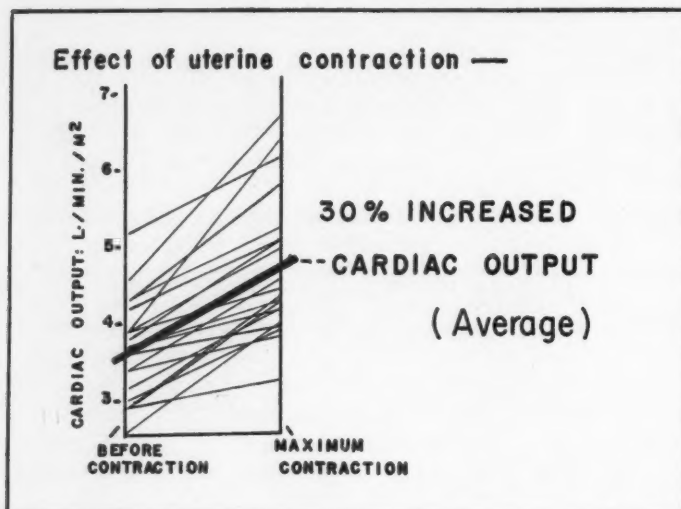


Fig. 3.—The increase in cardiac output associated with uterine contractions.

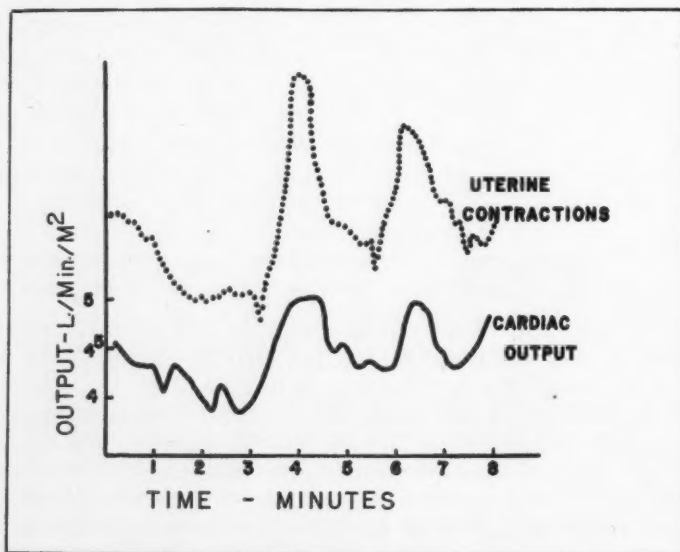


Fig. 4.—The effect of uterine contractions upon cardiac output.

A particularly illuminating tracing is seen in Fig. 5. The patient had established good labor clinically, and the cervix was 8 cm. dilated. Almost simultaneously, an initial injection of Metycaine was administered through a previously placed catheter, an arterial needle was placed, and the tokodyna-

momometer leads were attached to the uterine wall. Although only 10 c.c. of 1.5 per cent Metycaine had been given, the contractions became less frequent, fundal dominance was lost, and the rises in cardiac output were associated with uncoordinated contractions of either the fundus or the miduterine area. This is a matter which will receive further comment in subsequent discussion.

TABLE III. CHANGES IN CARDIAC OUTPUT ASSOCIATED WITH INEFFECTIVE UTERINE CONTRACTIONS

| PATIENT | CARDIAC OUTPUT/M ² PRECONTRACTION | CARDIAC OUTPUT/M ² HEIGHT OF CONTRACTION | PERCENTAGE INCREASE |
|---------|---|--|------------------------|
| J. L. | 3.84 | 4.20 | 9.4 |
| M. B. | 3.79 | 4.56 | 20.3 |
| J. J. | 2.21 | 2.60 | 17.6 |
| P. S. | 4.10 | 4.66 | 13.7 |
| P. S. | 4.16 | 4.86 | 16.8 |
| P. S. | 4.11 | 5.00 | 21.7 |
| P. S. | 4.37 | 4.72 | 8.0 |
| E. H. | 3.06 | 3.62 | 18.3 |
| E. H. | 2.92 | 3.73 | 29.5 |
| E. H. | 2.79 | 2.82 | 36.9 |
| Average | 3.54 | 4.18 | 19.2 |

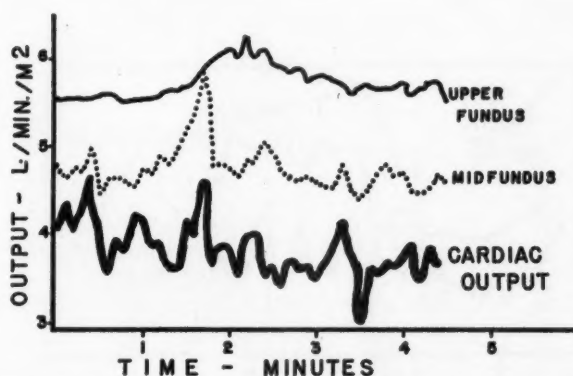


Fig. 5.—Effect of incoordinate uterine contractions upon cardiac output.

Another form of ineffective contractions is the type resulting soon after the administration of Pitocin. In the study of a small number of patients to whom Pitocin was given, it soon became evident that the cardiac output associated with contractions induced by Pitocin resembled more those of the ineffective than the effective uterine contractions. This may be true because most of the patients to whom Pitocin was administered were in labor already, but not making clinical progress at the time the testing was done.

Some of the more salient features of Pitocin-induced contractions are illustrated in Fig. 6. Perhaps the most striking feature of this particular study is the fact that this patient in late labor required so long to indicate either a tokodynamometer response or a cardiac output response to the drug. With the primigravid patient under caudal analgesia, crowning and prepared for delivery, $\frac{1}{15}$ minim of Pitocin was administered intravenously. A uterine contraction did not ensue for approximately 4 minutes, after which a prolonged tonic type of contraction occurred. This contraction was fairly typical of the tonic response ordinarily referred to clinically as a "Pitocin contraction." It was interesting to observe that there was no significant cardiac output response or change until the uterus began to contract, following which

the cardiac output also increased and maintained its elevated level for the duration of the tonic contraction. This would indicate that under these conditions the cardiac output rises due to changes in uterine contractility rather than from a direct effect of Pitocin on the cardiovascular system.

C. Other Factors in Labor.—

In the attempt to study the effects of labor upon the cardiovascular system, several factors other than uterine contractions are pertinent to consideration. These include bearing down, the effect of pain, and the effect of anxiety.

1. *Bearing down:* A voluntary or involuntary bearing down by the patient in labor constitutes essentially the Valsalva maneuver, wherein an increase in intrathoracic pressure impedes the return venous flow to the heart.

Two male subjects studied as controls followed a consistent response pattern. After deep inhalation, vigorous bearing down was accompanied by a sharp rise in arterial pressure which persisted for a few seconds and then fell to a reduced level. During the fall in pressure, there was a progressive decrease in pulse pressure. Exhalation produced a further sharp drop in arterial pressure, and in some trials there was a near disappearance of the pulse pressure for several beats thereafter. Subsequently both the arterial systolic pressure and the pulse pressure rose dramatically, and during this phase there was a marked bradycardia.

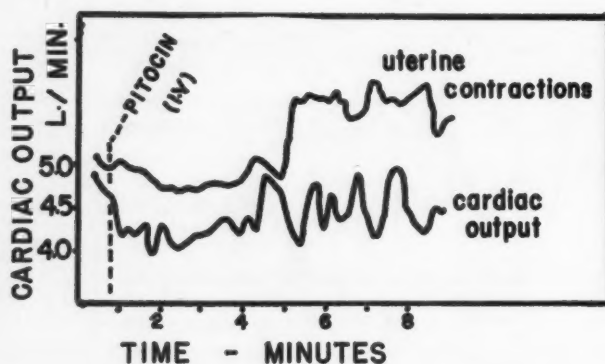


Fig. 6.—Cardiac output and uterine contractions as affected by the intravenous administration of Pitocin.

The cardiac output, as indicated by the pulse pressure method, consistently dropped sharply during the first few seconds of straining, but partially recovered toward the end of the bearing-down period due to increased pulse rate. After exhaling, there was usually a transient rise in output (corresponding to the "overshoot" period), and return to the base-line output was usually accomplished within one to two minutes.

A wide variability in the pattern produced by bearing down was observed when the study was extended to patients in labor. Straining down in the absence of a contraction usually resulted in a small to moderate transient drop in output, but in some cases there was a small rise. The acute changes in output during bearing down were usually smaller than had been the changes observed in the nonpregnant control subjects. During a uterine contraction, the pattern of response became even more atypical. For example, by bearing down with a contraction, one subject actually raised her output momentarily by 29 per cent, but dropped back to the "nonbearing-down" level within the next 12 seconds. The difficulties in interpreting output changes due to bearing

down during a contraction are many, since during a contraction the output may be changing rapidly quite independently of the bearing-down maneuver.

2. *Pain:* A measurement of the isolated effect of pain on the cardiac output is difficult during labor because pain is likely to be associated with other phenomena such as uterine contractions, which also significantly affect cardiac output. Some evidence was obtained along this line, however (Table IV). In one patient, after a prolonged delivery, the conduction analgesia level dropped rapidly toward the end of the episiotomy repair, leaving the skin edges susceptible to pain. Estimations of cardiac output made during the final suturing indicated rises of 21 and 15 per cent in cardiac output as sutures were inserted into the sensitive skin. Again, at cesarean section, the spinal anesthesia had not quite reached the optimum level by the time the surgeon was entering the peritoneal cavity. In this unpremedicated patient, stretching of the peritoneum resulted in acute pain, and the cardiac output rose by 24 per cent. In a third patient, the insertion of a needle intravenously for taking a blood specimen raised cardiac output by 15 per cent.

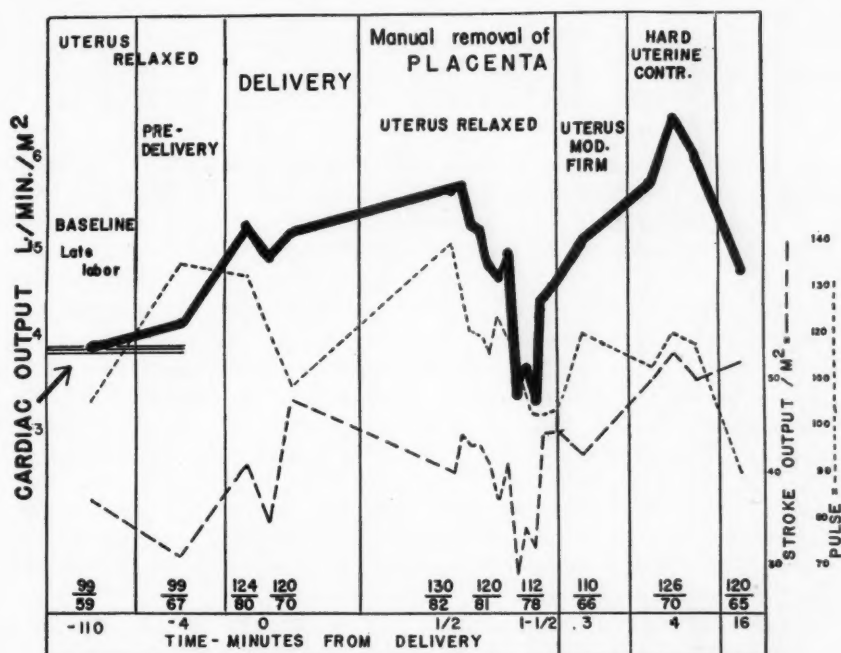


Fig. 7.—Changes in cardiac output in late labor, delivery, and post partum.

3. *Anxiety:* Again, the measurement of the anxiety factor during labor is rather difficult. The following evidence may be helpful. In 3 patients who had just received arterial punctures painlessly, and who were not having active uterine contractions, the initial cardiac output readings were 33, 61, and 11 per cent, respectively, above the output values they achieved after they were reassured and resting quietly.

D. Delivery and Post Partum.—

1. *General changes in parturition:* The cardiac output alterations associated with delivery and the early postpartum period usually include a significant rise in late labor, a further slight rise in some cases with delivery, and some variable changes post partum. Fig. 7 gives a graphic portrayal of the

TABLE IV. CHANGES IN CARDIAC OUTPUT INDUCED BY PAIN, ANXIETY, AND ELEVATION OF THE LEGS

| PATIENT | CONDITION | OUTPUT, BASE LINE (L/M ²) | CHANGE IN CONDITION | ALTERED OUTPUT (L/M ²) | PERCENTAGE CHANGE |
|-------------------------|--|---|--|--|----------------------|
| <i>Pain.</i> — | | | | | |
| L. J. | ½ hour post partum | 3.95 | Pain of suturing | 4.79 | +21 |
| | | 4.11 | Dropping caudal level | 4.74 | +15 |
| B. S. | Start of cesarean section | 3.78 | Stretching peritoneum; low spinal level | 4.68 | +24 |
| L. M. | Sedated; not in labor | 3.56 | Insertion of intravenous needle | 4.09 | +15 |
| <i>Anxiety.</i> — | | | | | |
| G. W. | Resting quietly | 3.53 | Anxiety at placement of brachial artery needle | 4.70 | +33 |
| J. J. | Resting quietly | 2.21 | Anxiety at placement of brachial artery needle | 3.55 | +61 |
| B. A. | Resting quietly | 4.14 | Anxiety at placement of brachial artery needle | 4.66 | +11 |
| <i>Leg elevation.</i> — | | | | | |
| M. R. | Second stage of labor; supine position. Caudal analgesia. No contraction | 3.8 | Legs up for delivery 1 minute; no contraction | 4.48 | +16 |
| L. M. | 37 weeks' gestation; not in labor | 3.35 | Legs up in lithotomy position for 1 minute (after 3 minutes) | 3.65 | + 7 |
| | ½ hour later | 3.43 | Legs up in lithotomy position for 1 minute (after 4 minutes) | 3.63 | + 6 |
| | | | | 3.40 | |

sequence of events in one case. While not exactly duplicating any of the other cases studied, this one is fairly typical, and is well documented in the sense that over 350 estimations of cardiac output were made during a three-hour period. Many of the findings are dramatic in degree. The changes will be discussed as percentage alteration from a base-line cardiac output, which was 3.91 L. per square meter of body surface in late labor. Nearly two hours later, just four minutes before delivery, the output had increased by about 6 per cent. During the actual process of forceps delivery, the output rose moderately, becoming about 34 per cent above the base level by the time the entire baby had been delivered. Thirty seconds later, the output had risen to 43 per cent above the base level. During the ensuing minute, a manual removal of the placenta was carried out. The uterus remained quite relaxed during this time, and the blood loss was minimal. The cardiac output dropped steadily to 17 per cent below the base-line level at one point, but by the time the separation had actually been completed the output had again returned to 15 per cent above the base line. Two minutes later, when the uterus was described as being "moderately firm," the output rose to 29 per cent above the base line, and after another half minute during which the uterus was observed to have become "rock hard," the output averaged 53 per cent above the base line. This excessively high output was not maintained, however, inasmuch as the level was stabilized at only 21 per cent above the base line twelve minutes later.

In summary, then, this patient had a mild output rise during the course of late labor, a moderate rise during delivery, a subsequent drop during manual removal of the placenta, and a sharp rise when the uterus became tensely contracted. The output returned to a range below that at delivery by 16 minutes post partum.

It has been postulated that the cardiac output rises post partum due in large part to the cessation of the maternal portion of the placental circulation. An attempt was made to demonstrate such an effect. In 5 cases of cesarean section and in 3 vaginal deliveries, manual removal of the placenta was carried out. Contrary to the expectation, it was found that of the 8 cases only 2 showed a significant rise immediately upon the removal of the placenta (11 and 20 per cent, respectively), while in the remaining 6 cases the immediate output following removal of the placenta remained essentially the same or dropped. In 8 cases, however, the output increased in some degree between $\frac{1}{2}$ minute and 2 minutes after removal of the placenta, the increase ranging from 1 to 41 per cent, and averaging 11 per cent (Table V). Within ten to twenty minutes the output values had returned in most cases to lower values, usually at levels lower than those prior to the removal of the placenta.

TABLE V. ALTERATIONS IN INDICATED CARDIAC OUTPUT DURING THE PROGRESS OF PARTURITION AND INTO THE EARLY PUERPERIUM

| PATIENT | PREDELIVERY. NO CONTRACTION (L./MIN./M ²) | JUST AFTER DELIVERY | BEFORE REMOVAL OF PLACENTA | IMMEDI- ATELY AFTER REMOVAL OF PLACENTA | $\frac{1}{2}$ TO 2 MINUTES POST PLACENTA | 10-20 MINUTES POST PLACENTAL |
|---------|--|------------------------|----------------------------------|--|---|---------------------------------------|
| M. Ra. | 3.3 | 3.15 | 4.0 | 3.01 | --- | --- |
| L. M. | 4.5 | 3.5 | 4.07 | 3.75 | 5.30 | 4.50 |
| B. S. | 4.6 | 5.5 | 5.40 | 5.40 | 5.45 | 4.50 |
| J. R. | 7.15 | 5.65 | 7.75 | 8.00 | 8.40 | 6.30 |
| J. J. | 3.42 | 3.19 | 3.09 | 3.42 | 3.59 | 2.92 |
| R. W. | --- | 6.50 | --- | 5.60 | 6.30 | 5.25 |
| P. S. | 4.00 | 4.08 | 4.10 | 4.00 | 4.30 | --- |
| L. J. | 4.50 | 5.23 | 5.60 | 4.44 | 5.04 | 4.72 |
| M. H. | 3.50 | --- | 3.26 | 3.90 | 4.00 | 3.8 |

No single patient was studied continuously through the entire labor and puerperium, but there were many patients in whom the relatively long study periods included the transition in time from early to late labor, from late labor through delivery, and so on. The findings in individual patients studied in the transition from one of these phases to another tend to bear out the impressions gained from a study of Table VI, where there appear the cardiac output values of a number of patients, averaged for different phases of labor and the puerperium. Starting in early labor, when the average output is 3.19 liters per minute per square meter, the level rises by 35 per cent among patients who are in late labor or who have had prolonged labor. A further slight rise to 37 per cent takes place when the patient is less than 1 hour post partum. In the group who were between 1 hour and 24 hours post partum, the rise above the early-labor base line was 22 per cent, while in patients 24 to 60 hours post partum, the rise was only 2 per cent above the base line of early labor. Although the use of such a table has severe limitations, as indicated in the previous discussion, the values given here may be at least helpfully indicative of the true situation.

TABLE VI. CARDIAC OUTPUT VALUES AT DIFFERENT STAGES IN PARTURITION. ALL RESULTS GIVEN IN LITERS PER SQUARE METER OF BODY SURFACE

| | EARLY LABOR | ADVANCED OR PROLONGED LABOR | LESS THAN 1 HOUR POST PARTUM | 1-24 HOURS POST PARTUM | 24-60 HOURS POST PARTUM |
|---------------------------------------|----------------|-----------------------------------|------------------------------------|---------------------------|----------------------------|
| | 3.55 | 2.90 | 4.00 | 3.20 | 3.02 |
| | 2.21 | 4.10 | 3.59 | 4.69 | 2.32 |
| | 2.99 | 4.16 | 2.92 | 4.84 | 2.25 |
| | 2.78 | 3.91 | 4.30 | 5.25 | 3.85 |
| | 3.10 | 4.37 | 3.80 | 3.47 | 4.82 |
| | 3.11 | 4.32 | 4.66 | 3.42 | |
| | 3.55 | 5.25 | 4.14 | 4.24 | |
| | 2.90 | 4.72 | 4.25 | 3.60 | |
| | 3.27 | 4.52 | 4.50 | 3.36 | |
| | 3.12 | 3.46 | 7.20 | 3.19 | |
| | 3.43 | 3.63 | 4.72 | 3.64 | |
| | 3.70 | 5.20 | | 2.54 | |
| | 3.71 | 4.31 | | 4.43 | |
| | | 4.26 | | 4.58 | |
| | | 4.06 | | | |
| | | 4.11 | | | |
| | | 7.15 | | | |
| | | 3.26 | | | |
| Average | 3.19 | 4.32 | 4.37 | 3.89 | 3.25 |
| Per cent increase over early labor | --- | +35% | +37% | +22% | +2% |

2. *Effect of lithotomy position at delivery:* The changing of the patient from the supine position to the lithotomy position produces interesting alterations in the cardiac output. In one patient (M. R.), for example, the changes were particularly striking. The patient, in labor and under caudal analgesia for some time, was allowed to lie in the delivery room in the supine position for about ten minutes, by which time she had made a good cardiovascular adjustment to the supine position, the indicated cardiac index being 3.8 L. Without otherwise disturbing the patient, who remained perfectly calm, the legs were quietly put up into stirrups. One minute afterward, the cardiac index had risen to 4.48 L., an increase of 16 per cent. Two minutes later, the cardiac index had dropped to 3.24 L., a decline of 28 per cent.

In two other observations performed on another patient, near term but not in labor, the placing of the legs into the lithotomy position increased the

cardiac output by 7 and 6 per cent, respectively. In both cases, however, the output had returned essentially to the previous base-line level within four minutes after the legs were put up.

Comment

A. Uterine Contractions.—

The uterine contraction is the basic unit of labor. The rapid, large, and consistent rise in cardiac output associated with the onset of an effective uterine contraction deserves discussion. It is believed that this increased cardiac output is a simple reflection of the fact that more blood has been presented to the heart, and therefore the output goes up provided the heart is well compensated. The apparent source of the blood is the uterus which, when contracting, squeezes a large proportion of its venous blood back into the central venous reservoir. The increased output is maintained until the contraction subsides sufficiently to permit not only the resumption of normal arterial circulation but also the accumulation of a normal complement of blood in the uterine venous system.

In short, the cardiac output rises sharply with the emptying of venous blood from the uterus, and drops again when the uterus relaxes sufficiently to allow the resumption of normal flow. Several pieces of evidence speak in favor of such an explanation:

1. It is common at cesarean section done on a patient in active labor to note that the uterus when tensely contracted has a blanched appearance, pink to almost whitish in color; while during intervals of relaxation it changes to a suffused purplish color. From appearance alone, it is not hard to visualize the "blanched contracted" uterus as having been largely emptied of blood, and the "suffused purplish" uterus as again containing an increased quantity of venous blood.

2. Woodbury and his co-workers¹¹ have demonstrated that at the height of uterine contractions in late labor, the intrauterine pressure may rise to such heights that it exceeds the brachial blood pressure, thus indicating that during this time the volume of blood which may have been squeezed out of the uterus into the systemic circulation cannot re-enter the uterus until it relaxes sufficiently to drop the intrauterine pressure below the arterial blood pressure level.

3. Perhaps the most illuminating bit of corroborative evidence along this line is the work of Palmer and Walker,¹² who made central measurements of the effect of uterine contractions on the circulation. They found that in the presence of even a mild uterine contraction, the arteriovenous oxygen difference is sharply increased, an increase which they interpreted as being due to the sudden addition of reduced blood from the maternal uterine circulation. A concomitant sharp rise in right intra-auricular pressure even during mild uterine contractions may be interpreted to mean an increase in the amount of blood which is being presented to the heart.

The small secondary rise in output after the first rapid drop while a contraction is subsiding is believed to represent the point at which the relaxing uterus, having become once more suffused with blood, begins again to contribute a normal amount of venous blood to the central circulation.

When we come to consider ineffective uterine contractions, or the contractions of incoordinate labor, the cardiac output responses have been found to be less consistent, less in amount, and of shorter duration. The implication is, of course, that such uterine contractions do not affect the entire uterus equally for their entire duration, and hence there is a variability in the quality and timing of uterine intensity as indicated by records from the various tographic leads.

B. Other Factors Associated With Labor.—

1. *Bearing down:* At first glance, it might be anticipated that voluntary or involuntary bearing down with a contraction should increase cardiac output, due to the increased work load. During the acute process of bearing down for a few seconds, however, this does not appear to be the case. Rather, the output follows, although with much variation, the pattern which might be expected from the performance of the Valsalva maneuver in the nonpregnant patient.

One reason for the large degree of variability in the response pattern is believed to be the changes in output inherent in labor itself. The ordinary changes due to Valsalva's maneuver are quite acute, and the entire exercise plus the subsequent reactive adjustments may be completed in less than a minute. In view of the previously demonstrated rapid changes in output due to alterations in uterine contractility, it should not be surprising that a uniform pattern has not been observed. Furthermore, the bearing-down effort of the patient in labor who is not experiencing any pain is likely to be more variable in quality and in duration than is the case with the nonpregnant volunteer subjects.

Despite the limitations of these observations, it may still be pertinent to add a comment concerning the actual increase in output which was associated with bearing down during the height of a contraction in some trials. The central venous reservoir is essentially a pool of blood largely contained within the thoracic cavity. The evidence, from both this paper and elsewhere,¹² indicates that with the onset of a uterine contraction there is a large transfer of venous blood from the uterus which must presumably raise the volume of the central venous reservoir before the additional blood is pumped through the heart. Thus, if the patient begins to strain down at the height of a contraction, there is likely to be a lag before the usual response to the Valsalva maneuver, i.e., the cardiac output will be maintained for a longer period than usual at a normal or even increased level because of the increased content of the central reservoir. This is a condition of intrathoracic venous congestion similar in some ways to pulmonary congestion associated with heart disease, in which there is also a prolonged maintenance of arterial pressure with straining.¹³ This process may be further accentuated if a uterine contraction (and the accompanying outflow of uterine blood) is beginning just as the patient begins to strain down, because in such a case the flow of venous blood into the thorax might be continued in spite of a moderate increase in intrathoracic pressure.

That the central venous reservoir actually varies in size with the stage of uterine contraction is indicated by the following case. In one patient (J. H.), dye dilution cardiac-output determinations were made in addition to the pulse pressure studies. With the uterus in the resting state, the central venous reservoir was calculated to be 376 c.c., while in a determination done during the early phase of a contraction, the venous reservoir was calculated to be 761 c.c. It seems justified, therefore, to assume that the state of uterine contractility may affect the response to voluntary bearing down.

The foregoing discussion deals, of course, with the acute response to bearing down, and points out that under varying conditions the cardiac output may be either transiently raised or transiently lowered at the time of straining. In a long-range sense, however, the act of straining down constitutes a vigorous form of work. Sampson¹⁶ has indicated that the patient who is bearing down frequently has a marked rise in oxygen consumption. It should be remembered that the reported rise in oxygen consumption during a series of vigorous voluntary efforts does not indicate the entire degree of added meta-

bolie effort, since the patient in late labor is running an increasing amount of her metabolic economy on an anaerobic basis, a fact not immediately reflected in a proportionately increased cardiac output.

2. *Removal of obstruction to venous return:* The release of the partial obstruction to venous return from the lower extremities has been considered by many an important factor in the production of a *postpartum* elevation in cardiac output. It has been believed that this change follows delivery, when the pressure of the uterus and its contents upon the great veins is relieved.

It has been demonstrated in this study, however, that the placing of the legs into stirrups *prior to delivery* removes the "obstructive factor," at least in a functional sense. McLennan¹⁴ showed that the venous pressure in the lower extremities reaches a height of about 15 cm. of water above the nonpregnancy level in the course of normal pregnancy, and that the venous pressure returns essentially to the nonpregnancy level immediately post partum. His determinations were done with the patients in the supine position. It has been further shown by Howard, Goodson, and Mengert¹⁵ that venous pressures in the lower extremity measured with the pregnant patient lying on the side instead of supine give values not greatly different from those obtained on nonpregnant patients. Such a finding helps to imply that the occlusive factor is primarily dependent upon the patient's position. It seems likely, indeed, that impeded venous return in association with pregnancy exists only when the patient is erect, sitting, or lying supinely; and that in all other positions the impedance factor is absent. Elevation of the legs into the lithotomy position raises the veins of the lower extremities far more than the 15 cm. required to overcome the impedance to venous return resulting from pressure of the gravid uterus against the great veins of the pelvis. Thus any increment in cardiac output resulting from increased venous return from the lower extremities should have been met even prior to delivery and, by the process of readjustment of the vascular bed, the increment should have been redistributed prior to delivery until it no longer constitutes a "surplus" quantity.

C. *The Work of Parturition.*—

In discussing the dramatic changes in output induced by volume redistribution and emotional states, we should not lose sight of the fact that one of the most basic reasons for changes in cardiac output is alteration in tissue metabolic demands upon the circulation. The actual work of labor, while discontinuous in nature, is not inconsiderable, particularly if labor is prolonged beyond the usual time. The finding in this study of a 35 per cent average rise in cardiac output in late or prolonged labor as compared to the level in early labor may well be significant along this line. Further evidence is that offered by Sampson, Rose, and Quinn,¹⁶ who demonstrated: (a) that "complicated deliveries were accompanied by a persistent elevation of oxygen consumption presumably caused by an increased circulatory load," and (b) that the maternal "oxygen debt" had not been repaid in some instances for one or more hours post partum.

D. *Postpartum Elevation of Cardiac Output.*—

Determinations of cardiac output performed during labor have not previously been reported. In spite of this fact, the statement has appeared in the literature, "Immediately following delivery there is another rapid increase in cardiac output amounting to 29 per cent."¹¹

The present study has demonstrated that: (1) during the intrapartum period there is an over-all rise in cardiac output, a rise which is particularly accentuated by some of the abrupt phenomena accompanying parturition; and (2) that cardiac output, already somewhat increased during labor, may or may not rise still further in the postpartum period.

The maintenance of increased postpartal output is probably not due to the presence of one or two factors, but of numerous factors operating simultaneously. Some potential contributing factors will be discussed sequentially, as follows: (1) blood loss, (2) removal of obstruction to venous return, (3) continued uterine contractions, (4) pain and emotion, (5) oxygen debt, (6) the need for diuresis.

1. Blood loss: It might be assumed that any significant degree of blood loss at delivery would tend to elevate the cardiac output, due to resulting anemia and the consequent need for augmented circulation. Within certain limits, however, this does not appear to be true. An exaggerated case in point is that of E. M. H., who was studied extensively both during the last part of labor and also, by a coincidence fortunate to this study, during the course of reaction to and adjustment from a postpartum hemorrhage. She had had a prolonged second stage of labor, nearly three hours, in which no clinical progress had been made, and the contractions had been noted to be of unusually poor quality. This patient's mean cardiac output index during late labor approximated 3.5 L. per minute. Immediately post partum, the mean output rose to 4.0 L. This level was not particularly affected by manual removal of the placenta, and it was noted that the uterus was not contracting down well. An atonic uterus persisted for 16 minutes post partum, during which the patient lost an estimated 800 c.c. of blood. The cardiac output remained surprisingly stable for the first six minutes in spite of steady blood loss. At the seventh and eighth minutes, a compensatory rise occurred (effected principally by a rising pulse rate), which was followed by a fairly sharp drop as the patient slipped toward shock, a level of 2.75 L. being indicated at one point. With the blood pressure remaining at near-shock level, a somewhat reduced pulse pressure was established and maintained, and the cardiac output became quite stable at about 3 L. per minute. At seventeen minutes post partum the uterus suddenly contracted effectively, and the cardiac output rose as suddenly to the range of 3.75 to 4.0 L., where it again became stabilized. (The patient had received only 100 c.c. of 5 per cent glucose intravenously by this time, as well as Ergotrate intramuscularly following delivery of the placenta, and Pitocin intravenously 10 minutes after delivery of the placenta). The patient subsequently did well, and did not require transfusion.

In summary, then, this patient's marked blood loss was not reflected in an increased cardiac output except for a transient rise just preceding the onset of her hypotension. It is felt that any output responses to acute blood loss at delivery will be made rather rapidly, as they were in this case, rather than being expressed as long-range elevations in cardiac output. Actually, the patient immediately post partum is being faced with a surplus of circulatory volume rather than a deficit, a surplus which may acutely embarrass the patient who is in precarious cardiovascular balance. Thus absence of blood loss at delivery would tend to maintain an elevated cardiac output, while a moderate amount of blood volume loss by the hemorrhage route—"uterine phlebectomy"—would work toward a lower, more nearly normal, output level.

An incidental observation in this case is of more than passing interest. It was noted that as soon as the patient's uterus contracted, the output returned to a normal postpartum rate, and the patient immediately felt better. The value of having the uterus contract was twofold: first, the blood loss was stopped, and, second, the atonic uterus, by contracting, "autotransfused" the patient, emptying perhaps several hundred cubic centimeters of blood suddenly back into the systemic circulation. The increase induced by such a contraction appears to be very much like the increase in output induced during an effective contraction in active labor.

2. *Removal of obstruction to venous return* has already been discussed, and is included here only for completeness. It is probably not a significant cause of the maintenance of cardiac output at any high level.

3. *Continued uterine contractions*: The changes in cardiac output associated with uterine contractions during labor appear to continue in modified form during the early postpartum period. Since the contractions are more prolonged, and the amount of blood involved in the uterine circulation is becoming progressively smaller, the pattern differs, but principally in degree rather than in its essential nature. In a uterine sense, it might be said that labor does not end with delivery, or with placental separation, or even within the first hour post partum, but is instead a process of slow regression taking place rapidly during the first hours post partum, with moderate speed during the first few days post partum, and even more slowly during the ensuing weeks. The cardiac output, of necessity, mirrors the circulatory aspects of uterine regression.

4. *Pain and emotion*: It has been shown that both pain and anxiety affect cardiac output in labor. Presumably both these factors as well as the well-known postpartum elation period might contribute to an increased output in the early puerperium. However, the postpartum patient usually is no longer experiencing pain, her anxiety is relieved, and the elation is a rapidly passing phenomenon. Such factors, then, are probably not important contributors to any sustained postpartum output elevation.

5. *The oxygen indebtedness* of the mother, in the absence of cardiac or pulmonary disease, is paid off, according to Sampson, in many patients by the end of the first hour. The excess of oxygen consumption after the first hour post partum, if present, is said to be small, indicating that this factor should be neither large nor permanent in maintaining any elevation in cardiac output in the postpartum period.

6. *The need for diuresis*: The association of water and electrolyte retention in the extracellular spaces in pregnancy—probably due to hormonal changes—is almost too well known to require comment. With delivery, the extra water and metabolites are available for excretion, and the classical postpartum diuresis is described as occurring between the second and fifth puerperal day.¹⁷

On the basis of evidence then available it was postulated by Starling,¹⁸ in 1896, that there should be a direct relation between renal excretory function and cardiac output. More recently, Borst¹⁹ has succeeded in accumulating further evidence to support this concept. Borst believes that diuresis by increasing cardiac function is a mechanism which operates independently from "the mediation of alterations in glomerular filtration and without the mediation of changing blood levels of adrenocortical hormones."

The concept that a "circulatory diuresis mechanism" may play some part in the postpartum elevation of cardiac output gains some indirect support from the fact that the period of elevation of cardiac output post partum and the postpartum diuresis, amounting in some individual cases to 3,000 c.c. per day, and averaging 2 Kg., in this diuresis period, coincide in time.

As might have been anticipated from this examination of the list of factors enumerated which could possibly contribute to a postpartum output significantly exceeding the antepartum cardiac output, the values during the first few hours tend to be particularly high, even when compared with the "postpartum plateau" level. The brief duration of such an elevated output appears to be due to the transient nature of most of the forces tending to elevate the

postpartum cardiac function. Adjustment to blood loss, if not excessive, can be carried out with surprising rapidity. The elation of delivery and the severe or constant pain usually pass off within a few hours. The "oxygen debt" of the maternal organism, which requires an increased circulation for repayment, is usually repaid within an hour post partum. Transient rises with postpartum uterine contractions become progressively less in their impact upon the circulatory system. And it has already been pointed out that the effective removal of the impediment to venous return from the lower extremities is probably largely accomplished simply by raising the legs as the patient is put up into lithotomy position prior to delivery.

Summary

1. In a study of 47 patients by a modified pulse pressure method, changes in cardiac output were recorded during late pregnancy, in labor, and in the early puerperium. This is the first report on cardiac output in labor.

2. During effective contractions in labor, the cardiac output rises an average of 30.9 per cent over the output in the resting state.

3. The act of bearing down in the absence of a contraction results in most cases in a small but transient drop in cardiac output. Bearing down with a contraction, however, may result in an actual increase in output.

4. Pain and anxiety can produce significant elevations in cardiac output.

5. Placental separation per se was not demonstrated to result in consistent variations in cardiac output. Contraction of the uterus post partum, however, may raise the output level significantly.

6. Cardiac output appears to rise during the first stage of labor, and may rise even further at delivery. In some cases a small additional rise is seen in the first few minutes post partum. The output persists at a moderately elevated level for a variable period thereafter.

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THE USE OF SPINAL ANESTHESIA IN OBSTETRICS AT THE EVANSTON HOSPITAL*

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IN RECENT years, the use of spinal anesthesia for obstetrical delivery has been the subject of much discussion in the literature. Although the majority of the reports are favorable, and although countless women, more than 50,000 of whose cases have been reported in the literature, have been delivered safely under this agent, nevertheless a few critical reports have served to dampen the enthusiasm of certain segments of the medical profession, and also of the laity. Notable among these are the reports of Rosenbaum and associates¹ who found 6 cases of residual paralysis among 1,272 patients delivered under spinal anesthesia in St. Louis, and Kennedy² who found 15 cases of residual paralysis following the use of this agent. In the first group the agent in 5 cases was dibucaine ("heavy Nupercaine"), an agent admittedly more toxic than others in general use today. The report states that the procedures were performed "under the close supervision of the resident staff. . . ." In Kennedy's cases the background is less clear. A number of critical reports prior to these two are thought not to be pertinent to this discussion, since they were published prior to the modern use of less toxic agents in hyperbaric solution. Also, the reports of death due to obvious overdosage of spinal anesthesia are thought similarly to be not pertinent.

In contrast to the frightening admonitions of Rosenbaum and Kennedy are the reports of Ottoway³ (5,276 deliveries under spinal anesthesia with no death or permanent injury), Watson⁴ (8,000 obstetrical deliveries under spinal anesthesia with no serious neurological complications), Crowder⁵ (1,000 deliveries under spinal anesthesia with no serious complications), Borel⁶ (9,000 deliveries under spinal anesthesia without any permanent neurological complications), and others. Of further interest in this respect is the report of Hingson and Hellman⁷ who, in studying 330 cases of maternal "anesthetic" deaths, found 155 due to aspiration of vomitus under inhalation anesthesia. There were 24 deaths under spinal (practically all associated with overdosage), 21 with caudal anesthesia, 49 with Pentothal sodium, 19 with Trilene, 25 under various general anesthetics, and 37 miscellaneous. Halperin and Levine⁸ also concluded that inhalation anesthesia takes first place in obstetric anesthesia death tables. Of 76 maternal deaths from anesthesia they found 53 under inhalation methods, 15 under spinal, and 6 with caudal anesthesia. Flowers⁹

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quotes Lull and Hingson as estimating that at least 2 per cent of maternal deaths result from the aspiration of vomitus. This accident can occur also under spinal anesthesia, but it can be prevented by the most elementary observation of the patient under regional block. Dripps and Vandam,¹⁰ after a follow-up of patients who received 10,098 spinal anesthetics, said, "Our experience indicates that the mortality rate following spinal anesthesia is lower than that recorded after general anesthesia in comparable patients undergoing comparable types of operations."

Results

From 1947 to the present date 15,202 patients have been delivered at the Evanston Hospital. Of these, 8,524 (56 per cent) were delivered under spinal anesthesia. Table I shows the increased use of the procedure. During the past 4½ years all hospital records have been systematically studied and all staff obstetricians have been regularly interrogated concerning complications of spinal anesthesia. Attending neurologists and internists have also been alerted to this continuing study. Rumors of complications have been painstakingly followed down to their apparent source. This pursuit has been a challenging combination of amateur sleuthing, diplomacy, and muted cross-examination.

TABLE I. INCIDENCE OF SPINAL ANESTHESIA IN OBSTETRICS AT THE EVANSTON HOSPITAL 1947-1955 (FISCAL YEARS)

| | TOTAL DELIVERIES | SPINAL | % SPINAL |
|-------|------------------|--------|----------|
| 1947 | 1,735 | 118 | 6.8 |
| 1948 | 1,466 | 345 | 23.6 |
| 1949 | 1,593 | 806 | 50.6 |
| 1950 | 1,586 | 1,105 | 69.7 |
| 1951 | 1,615 | 1,167 | 72.3 |
| 1952 | 1,732 | 1,143 | 66.6 |
| 1953 | 1,734 | 1,187 | 68.5 |
| 1954 | 1,854 | 1,336 | 72.1 |
| 1955 | 1,887 | 1,317 | 69.8 |
| Total | 15,202 | 8,524 | |

There were no deaths in this series of 8,524 cases. In 2 cases only was there disability which could be related to the spinal anesthesia. The first of these was a mild foot-drop which became evident the day after delivery. Four and one-half years later the patient still had moderate, but not disabling peroneal weakness. Its appearance following the use of spinal anesthesia suggests a causal relationship. Foot-drop has been recorded after general anesthesia,¹¹ however. The second was a case of paralysis of the sphincter ani which first became evident on the fourth postpartum day. This gradually improved and recovery was complete in 6 weeks.

The incidence of "postspinal headache" was 7 per cent. Of these, 10 per cent were classed as severe. These were positional in nature, generally being marked when the patient was in the upright position, vanishing almost entirely upon lying down. With rare exceptions, the headaches subsided entirely within 5 days of delivery. A complication which was frequent in the early cases of this series was sudden, marked hypertension with excruciating headache which followed within 1 or 2 minutes of the administration of intravenous Ergotrate after the delivery of the placenta. Conti and Natali¹² have described this syndrome when vasoconstrictors are followed by Ergotrate. In

our experience, even without prior vasoconstrictors, we have encountered this alarming syndrome with sufficient frequency to have discontinued the use of intravenous Ergotrate in patients who have received spinal anesthesia.

Technique

All obstetrical anesthesia is administered by fully qualified physician anesthesiologists. Spinal anesthesia is administered only upon the direct order of the obstetrician, and is not employed as a means of delaying delivery until such time as the obstetrician might reach the hospital from a distant point. In the latter circumstance the resident is instructed to proceed with the delivery. Spinal anesthesia is used as a terminal anesthetic which is administered only when the patient is ready for delivery. True saddle blocks are occasionally given, but for the most part the low spinal technique is employed, giving effective anesthesia up to the level of the tenth thoracic segment.

Proper positioning of the patient is important, and lack of attention to this detail may lead to the greatest difficulty in placement of the needle. The patient's back should be at the edge of the table, and in a vertical plane. The knees should be flexed upon the abdomen, and the chin flexed upon the chest. The presence of an assistant is mandatory to maintain good position in a woman experiencing labor pains.

The back is washed with soap and water, painted liberally and over a wide area with an alcoholic antiseptic preparation, and the area draped with 4 sterile towels. The lumbar puncture is then made between the third and fourth or fourth and fifth interspace, depending upon which appears to be more direct. Infiltration with procaine prior to introduction with the spinal needle has been found to be unnecessary. A 22 gauge needle is used routinely and is introduced into the subarachnoid space with the bevel of the needle cephalad. A solution of 0.5 c.c. of 1 per cent Pontocaine (5 mg.) and 0.5 c.c. of 10 per cent dextrose is slowly injected between uterine contractions. If the solution is injected during a contraction, the increased cerebrospinal fluid pressure at this time may cause rapid diffusion of the drug with unsatisfactory levels. After injection the patient is turned immediately upon her back, the head propped up with a pillow, and after a waiting period of 2 to 3 minutes preparation and draping begin.

Vasoconstrictor drugs are required only exceptionally. If, after the administration of the block, the condition of the patient demands the use of a vasopressor, ephedrine is given, and the obstetrician notified. The alarming hypertension which may follow the use of intravenous Ergotrate when vasoconstrictor drugs have previously been given has already been noted.

Most failures to obtain satisfactory analgesia are due to faulty technique, such as injecting the drug into the epidural space or partially into the subarachnoid space. Spotty analgesia may sometimes occur as a probable result of arachnoid adhesions preventing diffusion of the agent, or anomalous pockets in the dura which allow pooling in certain areas. Very occasionally a patient gets little if any effect from a technically satisfactory puncture. If within 10 minutes satisfactory analgesia does not appear we proceed immediately with general or local anesthesia. If the timing of the first block was properly chosen, it is too late for a second puncture to be made when it becomes evident that the first has been unsuccessful. Also, the amount of Pontocaine injected is twice the desired dose, and a serious hazard may be imposed if the first injection finds its way into the spinal canal. Finally, a second spinal block will rarely be more satisfactory than a first.

Comment

The two absolute and fundamental requisites for delivery under spinal anesthesia are an obstetrician who is sufficiently skillful to know whether this agent is applicable to the case in question, and to select the precise moment at which it should be given, and, second, a qualified anesthesiologist who is competent not only to administer the agent, but also to observe and evaluate the patient's reaction to it. It is a fallacy to presume that this anesthesia is applicable to all obstetrical patients. It is also a serious misapprehension to presume that anyone who can do a spinal tap is qualified to administer spinal anesthesia. Cole¹³ comments regarding spinal anesthesia that "it is entirely safe so long as it is considered to be a major medical procedure. Like any other form of anesthetic it can be dangerous by performing it recklessly and inviting disaster. I do not perform it lightly, nor do I attempt it without first preparing myself for the few untoward eventualities which I know may follow." This agent demands the same respect given other potent anesthetic agents, and should be given only by properly qualified anesthesiologists. Failing this, open drop ether or local infiltration is infinitely preferable.

There are certain contraindications which must be carefully noted:

1. A history of any disease of the central or peripheral nervous system, or any systemic disease which at some future date might affect the central nervous system, as for example pernicious anemia.

2. A history of back injury, pain, spinal fusion, or the like.

3. The obvious contraindications of hemorrhage, shock, hypotension, or severe hypertension.

4. A deep-seated fear, or a serious reluctance, on the part of the patient should be considered a strict contraindication.

5. Obstetrical contraindications: these include all obstetrical operations for which optimal uterine relaxation is necessary. It is debatable whether uterine tone is increased by spinal anesthesia. But it is certain that this agent does not relax the uterus.¹⁴⁻¹⁷ Hence, spinal anesthesia is contraindicated in any circumstance which might require uterine relaxation as, for example, version. Accordingly, spinal anesthesia is inadvisable in multiple pregnancy, where version may be necessary for the delivery of the second twin. In one of our early cases in which spinal anesthesia was used for delivery of twins, the cord of the second twin prolapsed through a very tight contraction ring in the mid-portion of the uterus. Deep ether anesthesia was required for the delivery of this baby, and stillbirth resulted. Similarly, in breech delivery we have encountered rings about the neck preventing engagement of the after-coming head, and hence consider this anesthesia undesirable in breech presentation. In the case of artificial rotation in persistent occiput posterior, an easy rotation will of course be easy under any anesthesia. But difficult rotations, requiring transabdominal manipulation of the shoulders, may be immeasurably facilitated by the uterine relaxation which accompanies general anesthesia.

If all of these admonitions are strictly followed, the results with spinal anesthesia in obstetrics should be good. Certain advantages of and indications for spinal anesthesia in obstetrics should be listed:

1. There is no depression of the infant by a terminal anesthetic which may augment the effect of analgesics required for the conduct of labor. There is evidence that this advantage is particularly marked in premature infants.¹⁷

2. Pain relief is instant. A patient who may have been excited and uncooperative prior to the spinal anesthetic immediately becomes tranquil and interested in the preparations which are being made for her delivery.

3. Bleeding during and after the third stage appears to be minimized by the increased uterine tone, in contradistinction to the relaxation which may accompany general anesthesia.

4. Aspiration of vomitus is a hazard in all obstetrical patients. This is virtually eliminated under spinal anesthesia. Hingson and Hellman's report of 155 maternal deaths from aspiration of vomitus during obstetrical anesthesia has already been cited. The last preventable maternal death at the Evanston Hospital occurred in 1948 and was due to this cause. It occurred under general anesthesia. Since this accident we have absolutely interdicted the use of inhalation anesthesia in any patient who has eaten within 4 hours, and prefer to avoid its use if the patient has eaten within 6 hours.

5. The incidence of operative delivery is not necessarily increased. In a consecutive series of 1,000 vaginal deliveries under spinal block, the incidence of spontaneous delivery was 61 per cent.

The question immediately arises whether one cannot obtain all the advantages attributed to spinal anesthesia, and avoid its purported dangers, merely by the use of local infiltration anesthesia or pudendal block. The two objections to this which make spinal preferable are, first, the fact that under local the patient is definitely less comfortable, as witness the fact that it is almost never used as a routine when other techniques are available, and, second, that the amount of time required for its administration very frequently makes its proper use not feasible.

Conclusions

1. Like any powerful drug, spinal anesthesia may be dangerous if it is given by unqualified individuals, without the most rigid attention to its proper administration, to its limitations, and to its contraindications. It is distinctly not an obstetrical panacea, and is not applicable to all cases.

2. In the literature, the overwhelming evidence is to the effect that, when it is properly and competently administered, spinal anesthesia imposes a hazard which is certainly no greater, and is probably less, than that of inhalation anesthesia.

3. The results in 8,114 obstetrical cases at the Evanston Hospital suggest (a) that the technique is safe; (b) that under certain circumstances it has distinct advantages over other types of anesthesia; and (c) that it is applicable to approximately 70 per cent of cases.

4. In a delivery room which is staffed with competent qualified anesthesiologists, spinal anesthesia is an extremely useful agent which should not be denied the patient merely because of the prejudices of the obstetrician.

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Discussion

DR. FRED B. HAPKE, Columbus, Ohio.—I was particularly delighted by the amount of time and emphasis which Dr. Burge placed on the relative safety of this procedure. I will admit that I am somewhat relieved by the fact that it stood up so well because it certainly is true that there have been numerous articles which have stressed and, I believe, exaggerated the dangers. Needless to say, I was pleased to learn that other investigators who have checked this phase of the problem have, for the most part, found this method relatively safe in comparison with general anesthesia.

In addition to stressing the safety of the procedure Dr. Burge mentioned on several occasions that these anesthetics should be given only by a trained anesthesiologist. I certainly agree that this is the ideal procedure, but I believe also that, it would greatly limit the usefulness of spinal anesthesia in obstetrics, because I doubt if many hospitals have an anesthesiologist who is continuously available. I believe that the obstetrician interested in this form of anesthesia can quickly acquire the ability to recognize complications and learn the method of management.

We started using spinal anesthesia in obstetrics at Ohio State University Hospital about 1947. At that time its primary purpose was to aid in some research which we were doing to evaluate the effect on the newborn of the various analgesic agents used in the first stage of labor. This evaluation naturally required the elimination of all forms of general anesthesia and low spinal seemed to be the substitute of choice. This means to an end, in our minds, soon became the method of choice for most of the service cases, and only those escaped who showed definite contraindications or were delivered before we could get to them with our needles. It was necessary that we in the Department of Obstetrics give our own anesthetics, and this policy has continued up to the present time. We have had no deaths and no complications more serious than the postspinal headache.

Upon entering into private practice it soon became evident that my policy on the use of spinal anesthesia would have to be modified and the percentage who now receive this method is considerably lower than it was on the clinical service. A part of this modification was necessary because of not having an anesthesiologist available and to do it ourselves requires considerable additional time and preparation. With a multiparous patient there often is not enough of either. Another factor was the varied fears of the patient of

permanent paralysis, or postspinal headache, etc. It has been my experience that to use spinal anesthesia extensively requires a rather intensive selling campaign.

And last, my personal philosophy has changed somewhat concerning the anesthetic of choice in any given case. In a primigravida where the various stages of labor are likely to be long and the delivery reasonably difficult, a spinal anesthetic can be a very gratifying experience from the mother's standpoint and a safer one for the baby. In a multigravida whose labor is short and delivery easy the advantages of a spinal are greatly overshadowed by even the rare occurrence of serious complications and the more common danger of postspinal headache.

We recognize that there are certain contraindications to and occasional complications with the use of spinal anesthesia in obstetrics. It is a technically simple and extremely reliable procedure when handled with care, however, giving good anesthesia in almost every case.

DR. WILLIAM J. DIECKMANN, Chicago, Ill.—The author favors spinal anesthesia for delivery and mentions deaths due to inhalation anesthesia. It must be remembered, however, that other types of anesthesia, including spinal, are not always successful and that inhalation anesthesia is usually the last resort. Furthermore, inhalation anesthetics such as ether are frequently given by an untrained house officer or an untrained nurse. On the other hand, the spinal anesthesia is always administered by someone with some experience.

In 1946, we began the use of spinal anesthesia in cesarean sections. We had always condemned it in obstetrical patients although we have used it for many years in gynecological surgery. In January, 1947, we began to use spinal anesthesia for deliveries and since that time have had over 12,000 low spinal or saddle block anesthetics without any maternal deaths. We know of one patient who developed a chronic arachnoiditis which was corrected by operation. Only about half of our patients return for postpartum examination, however, and we have no way of knowing whether there are other cases of nerve injury from spinal anesthesia.

In the period from 1931 to July 1, 1955, there have been over 82,000 obstetrical patients who were given some form of anesthesia. Over 70,000 of these patients received an inhalation anesthetic, with 3 deaths due to aspiration pneumonia.

One can find reports both for and against spinal anesthesia in obstetrics. In 1947, 49 per cent of our patients were delivered with low spinal anesthesia. In 1953 the figure was 38 per cent, but in 1955 it is again 49 per cent. On my own service I use spinal anesthesia when it is indicated as, for instance, after a recent full meal when the stomach cannot be emptied with a large tube, in the presence of a respiratory infection, a difficult delivery, etc. A certain number of patients are selected for training purposes.

I believe there are sufficient data in the literature as well as unreported studies of our own to indicate that spinal anesthesia is contraindicated in cesarean section, because of the increased neonatal mortality, especially if the baby is premature.

Local anesthesia has the best safety record. Inhalation anesthesia, if administered by a competent person, is next in safety. If no competent anesthetist is available, however, delivery should be by local anesthesia, with spinal anesthesia reserved for the complicated cases, the administration to be by the obstetrician.

DR. HARRY M. KIRSCHBAUM, Detroit, Mich.—In 1924, at the Wertheim Clinic, they changed from general to spinal anesthesia. The immediate postoperative mortality dropped from 12 to 5 per cent. When I returned in 1925 I started using spinal for delivery with forceps. I must say the patients were better, and the babies definitely were better. At that time, too, Delmoss of Paris stated that you could give a patient a spinal anesthetic, dilate the cervix manually, do a version, and go home. That was not successful because one tore the cervix.

The trouble was that Delmoss never examined the cervix. At that time I was examining the patients immediately after delivery, and doing extensive postpartum repairs,

such as repairing the rectocele, and doing a hemorrhoidectomy. It was designated by Dr. Topp, one of our interns, as the "All American."

Since 1930 I have done all the cesarean sections under spinal, but I did something a little different from what Dr. Burge did. The patient to whom I gave a spinal for delivery or for section was tested to see if she was sensitive to Novocain. Nupercaine is a more dangerous drug than Novocain, and so is Pontocaine. I am quite amazed at the big dose the doctor gives for the ordinary delivery. You need only 30 or 40 mg. of Novocain.

The question of fear is eliminated by putting the patient to sleep all during labor. In other words, it is my feeling that when the patient has pains every ten minutes and the cervix is dilated 2 cm., and if the pains are lasting 45 seconds in the primipara, she should be given medication and put to sleep, and the spinal used at the end. The doctors have given the spinal since 1930.

DR. BURGE (Closing).—It was largely through the efforts of our anesthetist that we began to try spinal anesthesia, and we became continually more pleased with it. I think Dr. Hapke is quite right—that patient acceptance makes a tremendous difference in any one locality. Perhaps the fact that we have put up mirrors so that the patients can watch the delivery if they choose has helped to make the patients in our area more interested in the method. We employ spinal anesthesia in cesarean section, with premature babies.

TRANSVAGINAL PUDENDAL NERVE BLOCK*

A Simple Procedure for Effective Anesthesia in Operative Vaginal Delivery

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LOCAL anesthesia for vaginal delivery is safest for both mother and baby. Despite the recent appearance of many articles describing the value of pudendal nerve anesthesia, many obstetricians and physicians in general medicine who practice obstetrics still do not employ this useful procedure. The simplified procedure that we are now using has, in a long trial period, proved an easily accomplished, effective method of anesthesia that is without danger of harm to the mother.

Pudendal nerve block was described by W. B. Muller in 1908, and in 1910 Ilmer¹ used this method in 50 obstetrical and gynecological cases. King² recommended it for normal deliveries and repair procedures. Urnes and Timmerman,³ Waldman,⁴ and Bunim⁵ described methods by which it is possible to infiltrate not only the nerve bundle in the region of the ischial spine, but also portions of the perineum superficially. About fifteen years ago we employed a pudendal nerve block procedure whereby perineal anesthesia was obtained by infiltrating only the area close to the ischial spines. In a manner similar to the techniques referred to, this area was infiltrated by first introducing a 6 inch, 20 gauge needle through the area midway between the anus and the ischial tuberosity. The needle point was then guided toward the ischial spine by the index finger, inserted into the rectum. Failure of adequate anesthesia regularly to ensue when the ischial spines were the only areas injected was discouraging, and a modification of the Bunim⁵ technique was adopted. This is essentially an infiltration of the anesthetic solution into the subcutaneous perineal and vulvar region, and also the pudendal nerve as previously described. This procedure has also been reported in many other recent articles on the subject of pudendal nerve anesthesia, and has been regarded as a dependable method. One could, perhaps, conclude that pudendal nerve block by injection through the perineal area has heretofore been regarded as unreliable without supplementary injections into the subcutaneous perineal region.

Recently there have been numerous reports of perineal anesthesia in which the use of hyaluronidase was included. Results appear to indicate that an anesthetic solution containing this enzyme diffuses more rapidly through tissues that heretofore have been difficult to penetrate. Baum⁶ therefore be-

*Presented at the Twenty-third Annual Meeting of the Central Association of Obstetricians and Gynecologists, Columbus, Ohio, Oct. 6, 7, and 8, 1955.

lieved that with the addition of hyaluronidase to the mixture, it is not necessary to deposit the anesthetic directly on the nerve itself, but in reasonable proximity to it. Moore⁷ suggested that the interval between nerve block and resultant anesthesia is shortened and that smaller volumes of anesthetic solution are required when hyaluronidase is used. Several previously encountered objections to pudendal nerve anesthesia are eliminated when hyaluronidase is added to the solution. Thus, Heins,⁸ Baum,⁶ Johnson,⁹ Griffin and Golkowski,¹⁰ and Douglas and Vosburgh¹¹ have found that this enzyme, employed in combination with procaine and epinephrine, induces an improved perineal anesthesia for an adequate period, with satisfactory tissue relaxation, and no distention of tissue in the operative field.

The term "pudendal block" has frequently been used incorrectly. True nerve block occurs when an anesthetic is injected adjacent to or into an arbitrary anatomical portion of the nerve bundle, and results in a temporary absence of painful sensations in the area supplied by this nerve. When the subcutaneous area of the perineum and vulva is also diffusely infiltrated as part of the so-called "pudendal block" procedure, the term becomes equivocal.

In a very scholarly presentation, Klink¹² has described the anatomical relations of the pudendal nerve, particularly with reference to the ischial spine. His procedure is truly a nerve block because it limits the area of anesthetic infiltration to the posterior aspect of the ischial spine. At this area the needle deliberately pierces the pudendal vessels. This is noted when blood is aspirated and thereby indicates the close proximity of nerve and area to be infiltrated. The anesthetic fluid is injected at three levels that are close together, namely, the lower and inferior tip of the spine, the upper or superior tip, and above this, the area of the greater sciatic notch. To reach the area of the ischial spine, the needle is inserted through the perineal skin in a manner very similar to the method previously described. The needle point, guided by a finger in the vagina, nevertheless traverses the ischiorectal fossa, a distance of approximately 10 cm. to reach its target. Klink uses lidocaine hydrochloride, 1 per cent, and does not use epinephrine or hyaluronidase.

During the past six years the senior author has developed and used a transvaginal method for achieving a pudendal nerve block. This procedure is simpler and has proved entirely harmless. The ischial spines are easily located through the vagina. When they are not prominent the sacrospinous ligament can be identified as a band of tissue in the sacrosciatic notch that converges upon the ischial spine. In palpating this important anatomical landmark, the mobile and elastic vaginal wall is brought into direct apposition to the ischial spine. The examining fingers touching this spine are now almost in direct contact with it and are very near to the pudendal nerve which is in close proximity to the posterior surface of the ischial spine. A needle inserted just below the point where the ischial spine is palpated will reach this area of the pudendal nerve with incredible ease.

Procedure

The materials recommended are: One 20 c.c. Luer-Lok syringe; one 6 inch, 20 gauge needle; 30 c.c. of anesthetic mixture containing 1 per cent procaine hydrochloride; 2 minims epinephrine, 1:1,000; 150 U.S.P. units hyaluronidase.*

Technique

The patient should be placed in the lithotomy position, prepared, and draped when delivery is imminent. For the primiparous patient this is when the cervix is completely dilated, for the multipara at 7 to 8 cm. dilatation. We prefer to initiate the procedure on the left side of the patient, primarily because we use the left hand in all vaginal or rectal examinations and our episiotomy incision is left mediolateral. To block the nerve on this side the



Fig. 1.—Shaft of needle placed in groove formed by apposition of index and large finger. Demonstration without gloves.



Fig. 2.—Same as Fig. 1, just prior to insertion of two fingers of left hand toward the region of the left ischial spine.

*The hyaluronidase used in this study was Wydase, supplied through the courtesy of Wyeth Laboratories, Philadelphia. A U.S.P. unit is defined as the amount of hyaluronidase which will reduce the turbidity produced by 0.2 mg. of potassium hyaluronate in acidified horse serum to that produced by 0.1 mg. under assay conditions.

left ischial spine is first palpated with one or two fingers of the left hand. If the spine is not satisfactorily identified it can be located by first feeling for the sacrospinous ligament. The entire procedure can be accomplished without any help. The needle should be tested for patency by forcing through it a small amount of anesthetic mixture, thus eliminating any air trapped therein. The shaft of this needle is then placed in the groove formed by apposition of the second and third digits of the left hand (Figs. 1 and 2). Guidance in this manner protects both the maternal and the fetal structures from inadvertent perforation. A diagrammatic sketch (Fig. 3) portrays the essential features of the technique we advocate. The needle directed laterally and downward penetrates the vaginal mucosa just below this bony projection. When it passes posterior to the tip of the spine the shaft of the needle is re-directed by lateral and downward pressure as indicated by the arrows. This makes the *direction of the needle one that is parallel with both the table and the*

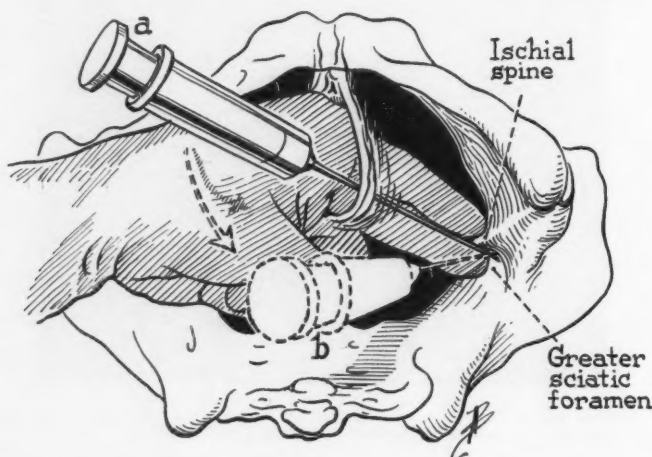


Fig. 3.—Diagrammatic sketch of transvaginal technique of pudendal block. *a*, The position of the syringe directed downward and laterally to pierce the vagina just below the projection of the ischial spine. *b*, The redirection of the needle to make it parallel with the table and the longitudinal axis of the mother as indicated by the arrows.

longitudinal axis of the mother's body (Fig. 4). As the needle is thus inserted, aspirate for gross blood. The pudendal vessels are close to the nerve in this area. If blood appears withdraw the needle to a level where it cannot be aspirated and then reinsert the needle deviated slightly medialward to avoid the vessels. The injection of the anesthetic is started about 3 cm. above the area of the ischial spine, which is in the greater sciatic foramen. Withdraw the needle slowly as the area is injected leaving about 3 c.c. to be instilled posterior to the ischial spine. When the needle has been withdrawn, gently massage the site of the vaginal penetration. For pudendal nerve block on the right side one can proceed as above, using the right hand to introduce the needle. After both sides have been injected, test for cutaneous sensation by a needle pricking or hemostat pinch. Do not proceed with the delivery until evidences of a satisfactory anesthesia are present on both sides. If, in three minutes, testing indicates that the anesthesia is still inadequate, reinject the area. In most instances there is almost an immediate loss of pain sensation. A large, butterfly-shaped area of skin anesthesia, reaching even to the adjacent thighs, may be observed in a short while. We have also observed that the bearing down pains disappear as they do with saddle block anesthesia.

Results

One hundred fifty-six cases were studied in the obstetrical department of the Cook County Hospital. The results were graded as excellent when the baby was delivered and the maternal tissues were repaired without pain. The result was regarded as good when it was necessary to reblock one or both sides but the anesthesia obtained was sufficient to complete the delivery and episiotomy repair. The result was recorded as poor when reblock of the nerve was not satisfactory, and/or where a supplementary local anesthetic had to be administered.

Using this grading, we studied three groups of patients who had a transvaginally administered pudendal nerve block. Best results followed use of a mixture that contained 1 per cent procaine, epinephrine, and hyaluronidase (Table I). When epinephrine was not included (Group B), pudendal block was of shorter duration, as indicated by evidences of pain when the skin margins of the episiotomy were sutured. Only 7 patients (a little over 4 per cent) needed repeated nerve block for a satisfactory result. Results were poor in 4 patients (2.5 per cent) in whom supplementary local anesthesia was required to complete delivery and perineal repair.

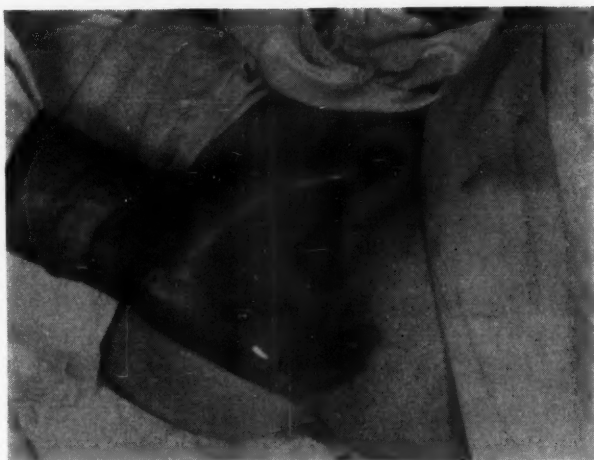


Fig. 4.—The needle redirected and inserted upward into the sacrocliac foramen.

Pudendal block by this method successfully met the challenge of all vaginal delivery procedures except version and extraction (Table II). In 3 of the breech deliveries, Piper forceps were used for the aftercoming head; these were classified with the low forceps deliveries. The midforceps group included 12 patients for whom the Kjelland forceps were used; 16 patients for whom the Scanzoni method of forceps rotation of the head was necessary; 3 patients in whom Barton forceps, and 2 in whom Tarnier axis traction forceps were used. The most prolonged pudendal nerve block lasted two hours. We have also noted that patients to whom analgesic drugs had previously been administered tended to have a more satisfactory pudendal nerve block anesthesia. If an assistant is available, a lateral angle retractor, such as that used in vaginal hysterectomy, can be employed, permitting direct visualization of insertion of the needle at the area of the ischial spine. This may be advisable for those who are learning how to use this technique. The transvaginal method of administering pudendal block anesthesia may be difficult when the baby's "head is crowning" and the mother has uncontrollable bearing down

TABLE I. RESULTS

| GROUPS | NO. OF PATIENTS | MULTIP- AROUS PATIENTS | PRIMP- AROUS PATIENTS | OPERATIVE PROCEDURES | EPISIOT- OMIES | NORMAL SPON- TANEOUS DELIVERIES | RESULTS | | |
|---|--------------------|------------------------------|-----------------------------|-------------------------|-------------------|--|-------------|------------|----------|
| | | | | | | | EXCELLENT | GOOD | POOR |
| A. Procaine | 17 | 8 | 9 | 14 | 10 | 3 | 12 (70.5%) | 4 | 1 |
| B. Procaine and hyaluronidase | 80 | 38 | 42 | 60 | 49 | 20 | 46 (57.5%) | 32 | 2 |
| C. Procaine, hyaluron- idase, and epinephrine | 59 | 24 | 35 | 48 | 45 | 11 | 49 (83.0%) | 9 | 1 |
| Total | 156 | 70 | 86 | 122 | 104 | 34 | 107 (68.6%) | 45 (28.8%) | 4 (2.5%) |

pains. In such instances a simple and rapidly administered local anesthetic will be sufficient for adequate episiotomy, and thus allow the mother to expel the baby normally. Some of the babies delivered were large; 2 weighed more than 11 pounds, and 2 weighed 10 pounds.

TABLE II. OPERATIVE PROCEDURES AND CONDITIONS

| | |
|-------------------------------------|-----|
| <i>Forceps.—</i> | |
| Low forceps | 81 |
| Midforceps | 35 |
| Total | 116 |
| <i>Other Operative Procedures.—</i> | |
| Episiotomy repairs | 104 |
| Third-degree extensions | 2 |
| Cervical repairs | 5 |
| Dührssen's incisions | 2 |
| Repair of ruptured vaginal stenosis | 1 |
| Repair of hematoma of vulva | 1* |
| <i>Miscellaneous Conditions.—</i> | |
| Abruptio placentae | 2 |
| Pre-eclampsia | 3 |
| Premature babies | 7 |
| Face presentation | 1 |
| Brow presentation | 3 |
| Fetal distress | 6 |
| Prolapsed cord | 2 |

*This patient had developed a hematoma of the vulva after delivery under transperineal nerve block. For evacuation of the hematoma and subsequent repair, a transvaginal nerve block was used.

Summary

In over 97 per cent of 156 patients who had transvaginal pudendal block, the anesthesia was considered good or excellent. Results were best when hyaluronidase was combined with 1 per cent procaine and epinephrine. At this point it is well to remember, however, the caution of Eckenhoff and Kirby¹³ that "addition of hyaluronidase to a local anesthetic is not a substitute for the proficiency of the anesthetist or surgeon in performing regional nerve blocks."

The transvaginal procedure for obtaining a pudendal nerve block has the following advantages:

1. Simplicity of performance. It can be carried out without aid.
2. The site of injection is nearest to the nerve to be blocked, affording greater accuracy in direct nerve infiltration.
3. The method is safe for mother and infant. No hematoma, infection, or other complication has been encountered in the past five years while this procedure has been used.

Addendum.—In the time intervening between the acceptance of our paper and this date we have used hyaluronidase with epinephrine in over 200 additional deliveries. The more often our residents applied this technique the better their results. The senior author in private and consultation practice has personally used this method of pudendal block in several hundred cases, but did not limit the type of anesthetic. The outcome in general was also very satisfactory. The persistence of good results is therefore essentially due to the procedure.

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Discussion

DR. CHARLES L. ALDRIDGE, JR., Grand Rapids, Mich.—Two years ago I first started to use the intravaginal route for pudendal blocks. I now am doing this type of block in about 90 per cent of all deliveries and believe that this method should be accepted as the technique of choice for blocking of the pudendal nerve. I am also convinced that the majority of men who try this technique would agree and soon come to prefer it.

There are several disturbing factors encountered with the transperineal type of block. First of all, there is the relative discomfort to the patient. The skin of the perineum and the levator muscle are both well supplied with pain fibers so that, even with the best technique, the patient must experience a moderate amount of discomfort. Second, when the needle has to penetrate skin and muscle, it is considerably more difficult to guide the needle to the pudendal nerve and the ischial spine. Third, and this may be a personal problem of mine, but I doubt it—not infrequently does the tip of the needle pass into the vaginal cavity accidentally.

With the transvaginal technique, all of these problems disappear. The patient experiences much less discomfort from the needle since the area of the vagina near the ischial spines, where the needle penetrates, is relatively insensitive to pain. The base of the spine is only a centimeter or two away from the point of penetration and therefore it is much easier to guide the needle tip accurately to the pudendal nerve.

Last, the problem of infection just does not seem to exist. The process of isoimmunization, or whatever keeps the majority of episiotomy wounds from becoming infected, is in effect. After all, not infrequently, the vaginal incision for episiotomy extends up to or above the point in the vaginal mucosa which is penetrated by the pudendal needle.

Our technique varies only slightly from Dr. Kobak's. One per cent Xylocaine (lidocaine hydrochloride) is used. A 10 c.c. Luer-Lok syringe is filled with solution and the needle is attached. After the spine has been located by one vaginal finger, the needle is laid along the palm side of the left forefinger (to block the left nerve) and guided into the vagina until the tip of the finger touches the tip of the spine. The needle is then advanced and the vaginal mucosa infiltrated with a small amount of solution. The needle is then further advanced not over 2 to 3 cm. and aspiration is attempted. If we happen to get blood, it simply indicates that we are in the pudendal vessels and near to the nerve. By withdrawing the needle slightly until we are out of the vessel and then injecting 15 to 20 c.c. we will get prompt blocking of the nerve.

I agree with the authors that this technique is effective for almost all types of vaginal deliveries including forceps and breech. We have found it unsatisfactory for any procedure which involves manual manipulation as in conversion of face presentations.

Another important contraindication is the attitude of the patient who is not psychologically able to accept delivery under any type of regional analgesia. Dr. Kobak did not mention the use of any other general agents for delivery. We have used nitrous oxide with contractions and have been gratified to find that there are an increasing number of women who can and want to remain awake during this type of delivery. There seems to be no contraindication to reblocking if the first attempt is unsuccessful. Occasionally

in these cases the legs will become numb because some of the agent reaches the sacral nerves. I have found many of my colleagues worried about using this technique when the head is low. This is indeed a problem occasionally. Even when the head is bulging or crowning, however, one is almost always able to insert a finger up to the spines between contractions. If this is impossible, then the patient certainly does not need a pudendal block for delivery and, as a matter of fact, the obstetrician will be lucky if he has time to do a local infiltration.

Again I would like to urge a more generalized trial of this effective and safe technique.

DR. MILTON L. MCCALL, New Orleans, La.—Our interest stems from the fact that Dr. Preston Wildes, in our Department, has been doing this for some year and a half. He has developed a somewhat similar technique and, I believe, quite independently. In fact, he tells me that in his perusal of the literature he has not been able to find any reference to this particular approach.

I would like to report that Dr. Wildes has personally used this technique in between 400 and 500 cases. He has had excellent success with it, without complications, to our knowledge. Some of you here may have heard his report before the District 7 meeting of the American Academy in Birmingham last spring. Dr. Wildes' technique is not very different from that described today.

First of all, the locations are identified on either the right or left side, and the sacrospinal ligaments are palpated. Following this, the needle is inserted. We bend the needle slightly and angle it in more directly than does Dr. Kobak, apparently. The end of the needle is on the wall of the index finger so that when the sacrospinous ligament is reached the finger is moved and the needle straightens out and goes directly into the ligament.

Then 3 c.c. of the anesthetic agent is presented into the ligament itself. We do this because the inferior hemorrhoidal nerve is aberrant in about 40 per cent of the cases. Then, with a little further pressure, there is a sudden "give" of the needle through the sacrospinous ligament, and at that point after aspiration the rest of the 10 c.c. of anesthetic agent is injected into this space.

I think there is one advantage to this method. It is very simple to make a re-injection vaginally. You go through such a small amount of tissue that reinjection is not a great problem.

Dr. Wildes' conclusions are these: Transvaginal pudendal block is a simple technique. He feels that this is probably much easier to learn. It is performed with dispatch by almost everyone who has used it on our service. Now a number are using it, and it does give rise to less discomfort to the patient.

Its reliability, of course, depends upon accurate placement of the needle, but we feel this is not difficult to do. As a matter of fact, about 85 per cent of our patients have had perfect anesthesia and have not had to have the injection repeated.

Hexylecaine is the most satisfactory agent we have used to date and gives the most prolonged anesthesia. Hyaluronidase speeds the onset of anesthesia but shortens its duration. Dr. Wildes feels that the conventional perineal approach is still preferable when the presenting part distends the perineum or when the sacrospinous ligaments are difficult to palpate.

We feel at the present time that the transvaginal approach is indicated not only in the second stage of labor but that it also has a real indication post partum for the relief of pain, and as gynecological anesthesia, especially in older women on whom vaginal procedures are to be done. In fact, we have used it successfully in one case of a radical vulvectomy in a very elderly woman.

DR. KOBAC (Closing).—Concerning the use of procaine with hyaluronidase, we have used those two, and the duration of the anesthesia was inevitably much shorter due to the rapidity of absorption by the use of hyaluronidase. When you use a combination of procaine, hyaluronidase, and epinephrine, however, you then get a prolongation of the anesthesia due to the fact that the epinephrine retards the resorption.

IRREGULAR SHEDDING OF THE ENDOMETRIUM*

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THE term "irregular shedding of the endometrium" is used to describe a type of functional bleeding characterized by prolonged and profuse menstrual flow. The diagnosis is made by histologic examination of endometrial tissue obtained by curettage at least five days after the onset of menstruation. Normally, at this time, regeneration of the surface endometrium is occurring and the microscopic picture is that of an early proliferative endometrium. In irregular shedding, regeneration of the surface epithelium is incomplete or absent. The endometrial glands in some areas show evidence of secretion and often assume the form of a star or other bizarre patterns. The stroma is contracted and dense in some areas and loosely arranged in others. Groups of thickened spiral arterioles are often found in abnormal numbers in the region of the retained glands.

The literature has been reviewed previously by Jones,¹ McKelvey,² and recently by Thierry.³ The condition was first described as prolonged and incomplete shedding by Driessen¹⁸ in 1914. In the next two decades, descriptions were made by other workers on the continent, notably Pankow,⁴ Kaufman and Hoeck,⁵ Baniecki,⁶ and Robert Meyer.⁷ Since 1935, reports have been made in this country by Traut and Kuder,⁸ Jones,¹ McKelvey,^{2, 9} Holmstrom,¹⁰ and McLennan.¹¹ The largest series of patients with irregular shedding was reported by Rockstroh.¹² His collective review included 640 patients from the Woman's Clinic in Berlin and 54 cases from the Woman's Clinic in Halle. The largest series of patients in this country was reported by McLennan who, after eliminating questionable cases, reported 49 patients with characteristic clinical and histopathologic findings.

The diagnosis of irregular shedding requires curettage of the entire uterus not earlier than the fifth day and preferably later. Endometrial biopsy will not produce sufficient tissue for diagnosis. The practical difficulties involved in timing the curettage to this late portion of the bleeding period probably accounts for the infrequent recognition of this condition. Only in centers where the diagnosis has been sought have sufficient cases for study been recognized. For this reason, the exact incidence is unknown but has been estimated by various authors as between 10 and 17 per cent of all cases of functional bleeding.

*Presented at the Twenty-third Annual Meeting of the Central Association of Obstetricians and Gynecologists, Columbus, Ohio, Oct. 6, 7, and 8, 1955.

This report is concerned with the experiences at the University of Minnesota Hospitals during the last 14 years. During this period a total of 152 patients with menorrhagia have had diagnoses of irregular shedding following dilatation and curettage. Twenty patients with the histologic diagnosis of this condition were eliminated from the study because the curettage was improperly timed or because the tissue diagnosis was questionable. Of the remaining 132 patients 33 were selected as having typical cases of irregular shedding. These patients gave a history of prolonged menstrual periods at regular intervals without intermenstrual bleeding and without previous gynecological surgery or demonstrable associated pelvic pathology. The remaining 99 patients are used for comparison and are designated as showing atypical examples of irregular shedding. The term "atypical" as used here does not apply to the histologic diagnosis but is used in that group of patients in whom coexisting conditions might contribute to the production of abnormal bleeding.

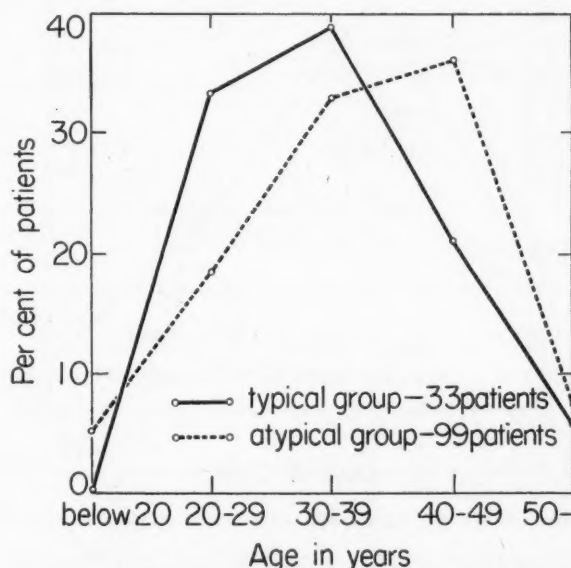


Fig. 1.—Age incidence in irregular shedding at onset of symptoms.

Characteristics of Irregular Shedding

Age at Onset.—Previous reports have agreed that irregular shedding can occur from menarche to menopause. Rockstroh found that the incidence increased from 1 per cent below the age of 20 years to 45 per cent in the 40 to 50 year age group. McKelvey also found an increasing incidence with advancing age. McLennan found an even distribution among the three decades between 20 and 50. Fig. 1 illustrates the age distribution at the onset of symptoms in this study. The peak incidence in the typical group is in the fourth decade and that of the atypical group in the fifth decade. The spread for the entire group is fairly uniform throughout the childbearing years.

Menstrual Complaints.—Although prolonged menstrual bleeding was characteristic of all cases, a reasonably accurate estimate of duration was not possible in 19 of the atypical cases. Fig. 2 illustrates the length of flow in the two groups. In the patients with typical irregular shedding, about 50 per cent

flowed from 8 to 10 days and about 25 per cent from 11 to 15 days. The atypical group showed a fairly uniform distribution of patients in regard to length of flow. The largest number of patients fall into the group who flowed for 16 days or longer.

The menstrual flow was described as profuse in 72.7 per cent of the typical patients and in 46.4 per cent of the atypical patients. Dysmenorrhea was associated with the onset of irregular shedding in 12.1 per cent of the typical and 13.1 per cent of the atypical patients. Irregular bleeding occurred in 31 patients, or less than one third of the atypical group. The menstrual interval was said to be shortened in 8 (24.2 per cent) of the typical and 12 (12.1 per cent) of the atypical patients. No instance of lengthened interval was noted in the typical group. Anemia of from mild to severe degree was found in 17 (51.4 per cent) patients with typical and 32 (32.3 per cent) with atypical irregular shedding.

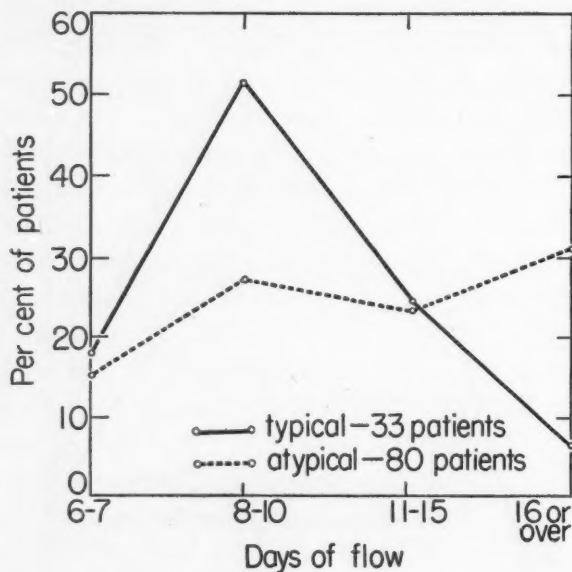


Fig. 2.—Length of menstrual flow in irregular shedding.

Fertility.—No past history of infertility has been described in the literature in relation to irregular shedding. On the contrary, the patients in this series demonstrated a high degree of fertility preceding the onset of their menstrual difficulties. In the typical group, 31 patients had a total of 182 pregnancies and 139 living children, an average of nearly 6 pregnancies per patient. Two patients of the typical group were nulligravidas, 26 and 33 years of age. The 26-year-old patient was the only one in the typical group known to have an infertility problem. The atypical group demonstrated a similarly high degree of fertility in their past history.

The degree of fertility following the onset of irregular shedding has not been determined although at least 5 of 13 patients in the typical group under the age of 35 years are known to have become pregnant following the onset of this condition. Two of these five patients are known to have become pregnant despite persistent menorrhagia.

Relationship of Onset to Pregnancy.—The onset of symptoms followed pregnancy closely in 12 patients of the typical group. In 2 of these patients the onset was dated from early abortion and in the remaining 10 patients

from term delivery. McKelvey has noted this relationship previously and believes that this represents a continuation of the irregular shedding type of bleeding commonly seen with the first menstrual period after delivery. In 5 patients the onset followed the third pregnancy and in the remaining 7 patients from the fifth to the eleventh pregnancy. McLennan found that this time factor was not a striking relationship in 90 per cent or more of the patients in his report.

Associated General Disease Processes.—An interesting finding in this study is the history of partial or complete thyroidectomy in a total of 15 patients. The typical group contains 7 (21.2 per cent) while the larger atypical group contains 8 (8.1 per cent) of these patients. Thiery reported 3 (13.6 per cent) previous thyroidectomies in his study of 22 patients with irregular shedding.

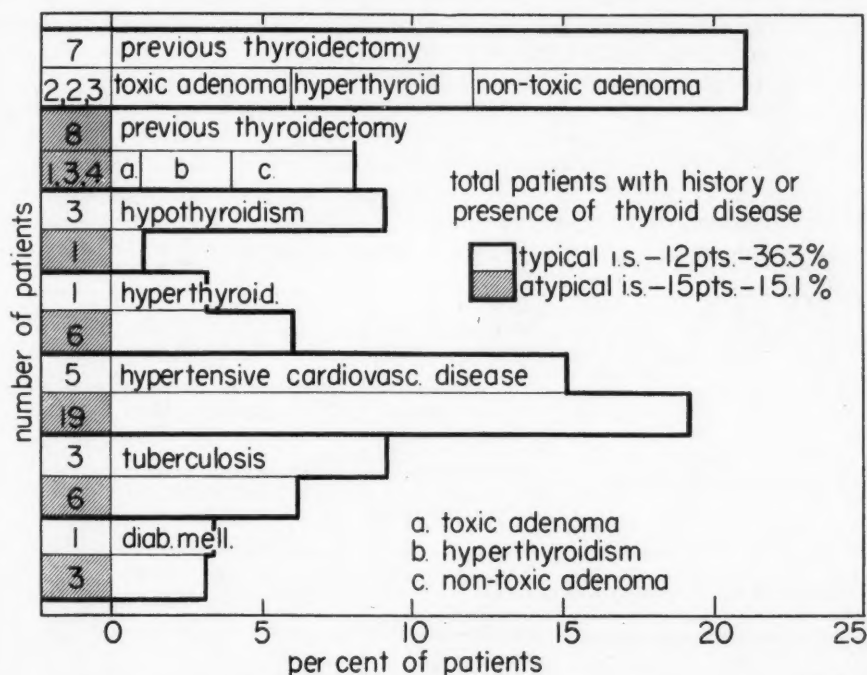


Fig. 3.—Associated medical diseases in patients with irregular shedding.

Fig. 3 illustrates the incidence of associated disease processes in the patients of this study. Hypertensive cardiovascular disease was present in 5 (15.1 per cent) patients in the typical group and in 19 (19.2 per cent) patients in the atypical group. Other disease processes found in smaller numbers of patients included hyperthyroidism, hypothyroidism, tuberculosis, and diabetes.

Associated Gynecological Disease.—In the atypical group of 99 patients the history of previous ovarian surgery was obtained in 16 patients. On examination under anesthesia at the time of curettage, the uterus was found enlarged in 33 patients. The criteria for enlargement consisted of either a notation by the examiner or findings of uterine depth greater than 3½ inches on sounding of the uterus. Myomas of the uterus were palpated in 24 patients and described as submucous in 8 patients. Adnexal pathology was found in 9 patients of whom 5 gave a history of pelvic inflammatory disease.

On histologic examination, local hyperplasia of the endometrium was found in association with irregular shedding in 12 patients, adenomyosis in 4, endometrial polyp in 6, and endometritis in 3. A group of 28 patients had

curettage for other bleeding episodes, either before or after the diagnosis of irregular shedding was made. In 11 of the 28 patients, hyperplasia of the endometrium was found. This high incidence of hyperplasia suggests a common etiology for the two conditions in some instances. Of these 11 patients, 2 were placed in the typical group, and 9 in the atypical group.

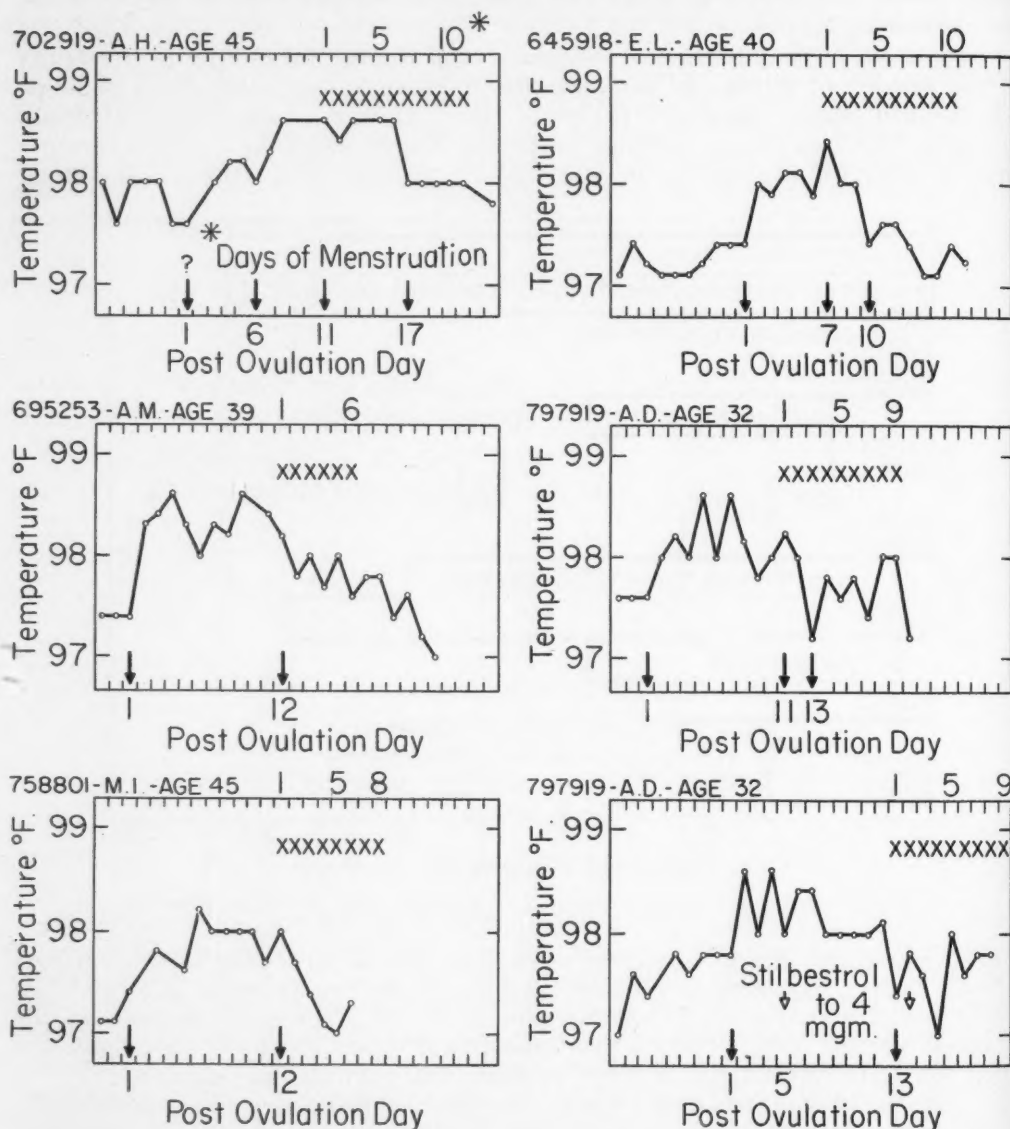


Fig. 4.—Basal temperature records of patients with irregular shedding.
*indicates day of menses.

Associated Pathology on Hysterectomy.—Pathology reports on 13 patients who had hysterectomy after the diagnosis of irregular shedding showed myomas in 3, basal hyperplasia of the endometrium in 2, adenomyosis in 3, follicle cysts of the ovary in 2, endometrial polyp in 1, postpartum subinvolution in 1, and carcinoma of the cervix in 1 patient. In 3 of the 13, no associated pathology was found. Of these 3 reports, 2 were from patients in the typical

group. One patient was operated on on the twenty-third day of her menstrual cycle. The endometrium was found to be early secretory and the corpus luteum in the vascular stage and considered to be in regression.

Basal Temperature Records in Irregular Shedding.—A small group of patients with irregular shedding who had persistently prolonged and profuse periods were studied in a special clinic in the outpatient department of the University of Minnesota Hospitals. These patients were instructed in the use of basal temperature records so that estrogenic therapy could be administered in the postovulatory phase with controlled timing. In 5 patients with satisfactory temperature records, the initial record taken without therapy showed a consistent deviation from normal during the first few days of menstruation. The temperature elevation was found to persist for one to six days into the bleeding phase instead of dropping before the onset of bleeding. Fig. 4 illustrates the temperature records in these patients. With the exception of the record of A. H., the total length of temperature elevation was not prolonged beyond the usual 12 to 14 days. The basal temperature record of A. H. is difficult to interpret because the temperature rise is gradual. This characteristic persistence of the temperature rise into the bleeding phase was previously reported by one of us and has since been described by Gillam¹⁴ as characteristic of irregular shedding. In 1945, Nieburgs¹⁵ reported that in menorrhagia the basal temperature does not fall as it normally does in the premenstrual period but remains at a high level into the bleeding phase.

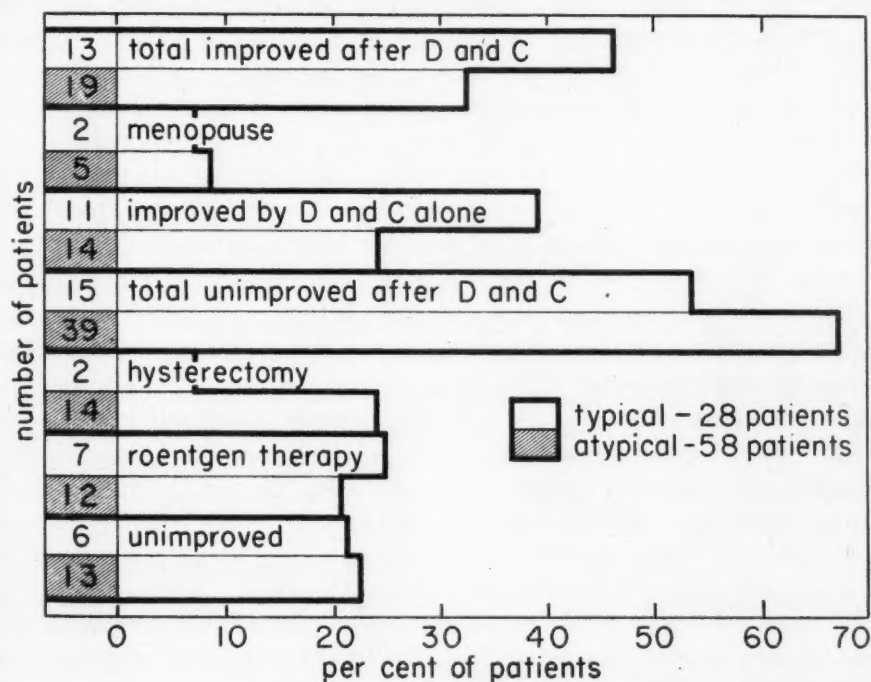


Fig. 5.—Follow-up of patients with irregular shedding.

Follow-up and Treatment

Follow-up was possible on 86 patients, 28 patients in the typical group and 58 in the atypical group. A total of 13 (46.4 per cent) patients of the typical group and 19 (32.7 per cent) of the atypical group were improved or cured after curettage. The patients who were improved include 7 women who be-

came menopausal shortly after curettage. The unimproved group includes 15 (53.6 per cent) of the typical group and 39 (67.3 per cent) of the atypical. Of these unimproved patients, a total of 35 required roentgen sterilization or hysterectomy for control of the bleeding.

Our experience with hormone therapy has been limited and necessarily empirical. We have favored the use of estrogens started one week premenstrually and continuing through the third day of menstruation. Diethylstilbestrol, 1.0 mg. and increased as tolerated to 3.0 mg. daily, has been effective in both clinic and private patients in diminishing the amount of flow, although the length of the bleeding periods was not appreciably affected. Fig. 4 includes the basal temperature record of A. D., aged 32, para iv-i-0-iv, who had continued to have profuse prolonged periods since curettage 18 months before. This period, the first following stilbestrol therapy, was described by her as the lightest flow she had experienced since the curettage. She was observed in the study clinic for over a year and had a normal amount of flow during the periods preceded by stilbestrol therapy but reverted to profuse flow when the stilbestrol was stopped.

Comment

In this study the 33 patients with classical symptoms of irregular shedding and without associated gynecologic pathologic conditions were separated from the larger group of 99 patients to evaluate better the clinical findings. From the comparison of the two groups, the differences appear to be no more than would be expected from the associated pathologic entities. The typical patients are on the average younger and have regularly recurring periods which are more uniform in length and more often profuse. Both groups have a high incidence of associated medical disease, particularly thyroid disease and hypertensive cardiovascular disease. The typical group shows an unusually high incidence of previous thyroidectomy and an unusual fertility rate. About one half of the typical group were improved by curettage while only one third of the atypical group were helped.

The characteristic findings described in relation to the basal temperature record indicate that the onset of bleeding occurs earlier in the corpus luteum phase than would be expected and that progesterone is present into the bleeding period. This finding agrees with those of McKelvey and Samuels,¹⁹ who demonstrated persistence of pregnanediol excretion during the bleeding phase in irregular shedding. Holmstrom and McLennan¹⁰ were able to reproduce the clinical and histologic changes of irregular shedding by giving progesterone to normal women during the early part of menstruation. Brewer and Jones¹⁶ concluded from the study of operative specimens of uteri and ovaries that the life of the corpus luteum may be prolonged without alteration of gross characteristics and without evidence of cystic change. In response to this prolongation of corpus luteum effect, the endometrium evidenced the characteristic changes of irregular shedding.

These findings would indicate that the corpus luteum at the end of its relatively uniform life span may be slow to regress and that there is a continuation of progesterone effect on the endometrium. If our limited experience with basal temperature records is correct, however, the total life span of the

corpus luteum as evidenced by the thermogenic effect of progesterone is not prolonged but continues into the bleeding phase due to break-through bleeding that occurs while the corpus luteum is still functioning. Masters and Magallon¹⁷ were able to produce break-through bleeding in menopausal women from varied dosage of progesterone after priming the uterus with estrogen. They found that the histologic picture of irregular shedding could be produced by progesterone levels simulating the normal course of the corpus luteum phase.

Break-through bleeding implies failure of the corpus luteum to support the premenstrual endometrium. Since the progesterone levels are not diminished during the early bleeding phase in irregular shedding as evidenced by normal pregnanediol levels and normal thermogenic effects, the premature onset of bleeding may be due to abnormal endometrial response to progesterone. Much remains to be learned about the abnormal bleeding mechanism in irregular shedding of the endometrium and, until more information is available, hormone therapy must remain on an empirical basis. The hemostatic effect of estrogen therapy is meanwhile useful in this as well as other types of dysfunctional bleeding.

Summary

This report includes an analysis of the clinical records of 132 patients with the diagnosis of irregular shedding of the endometrium by curettage timed to the fifth day or later of the menstrual period. The entire group was divided into a smaller group of 33 patients who had classical symptoms of irregular shedding without associated gynecologic pathology and a larger residual group of 99 patients who are designated as having atypical symptoms. Comparison of the two groups reveals differences that for the most part can be explained by the presence of associated pathology. We agree with previous observers who feel that irregular shedding is a clinical entity that may exercise its dysfunctional effect with or without associated gynecologic pathology.

A group of 5 patients were observed in a study clinic with basal temperature records employed as a control for estrogenic therapy. Review of the temperature records before therapy showed that bleeding occurred earlier in the corpus luteum phase than is normally expected. This is interpreted as break-through bleeding possibly due to abnormal endometrial response to normal progesterone levels. Postovulatory stilbestrol therapy was employed with good hemostatic effect but without shortening the length of the bleeding period.

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Discussion

DR. BEN M. PECKHAM, Chicago, Ill.—It has been repeatedly demonstrated that dysfunctional uterine bleeding, a term preferable to “functional” uterine bleeding, may be associated with any type of endometrium from atrophic to secretory or hyperplastic. The authors deal here with patients in whom the relating factors are menstrual endometrium with secretory changes, obtained on the fifth or subsequent day of bleeding, which was either profuse, prolonged, or both. Their two groups differ only in that the latter patients were on the average slightly older and had local pathology in the pelvis. They consider this division probably to be artificial and believe that the abnormal bleeding is most likely dysfunctional rather than caused by the pathologic conditions. With this opinion I would agree in general, but doubt that it is justified with regard to the 8 patients who had submucous fibroids if these tumors were polypoid or significantly distorted the uterine cavity.

The authors, on the basis of admittedly limited temperature curve data, favor the “break-through” bleeding explanation first suggested by Masters and Magallon except that they believe the endometrium is most likely at fault rather than some abnormality in the corpus luteum since pregnanediol excretion has been shown by others to be relatively normal in this type of patient. From their data it appears, however, that the break-through explanation can hold for only about 15 per cent of patients as only 20 of the total 132 were noted to have a shortened menstrual interval (which would have been expected if break-through occurred).

The work of others, McKelvey and Samuels, Holmstrom and McLennan, and Brewer and Jones, suggests that prolongation of the life of the corpus luteum is a more common cause. Brewer and Jones on the basis of their studies of whole uteri and the associated corpora lutea point out the variations in endometrial phase or response seen in different areas in the uteri of some of these patients. These observations support the authors' suggestion that the important factor is a local endometrial one in some of these cases. Perhaps this is just an increase in patchiness beyond that seen in normal menstruation though this would not explain the symptom of excessive bleeding seen in many of these patients.

I am confused by the authors' exclusion of all cases not conforming to their microscopic definition of this condition yet inclusion of 12 cases of “local hyperplasia of the endometrium.” I would have expected that in those patients curetted on the fifth or sixth day and due to finish bleeding on the following day (18 per cent of these 132 patients are recorded as bleeding six to seven days) regenerating proliferative endometrium would have been found but not endometrial hyperplasia if we are speaking of the same condition.

Curettage is required for diagnosis in these patients and is reported here to bring about improvement in 30 to 50 per cent of patients. Previous or repeat curettage was performed in 28 patients. In eleven of these 28, endometrial hyperplasia was found. The authors state that this suggests a common etiology for the two conditions. This seems unlikely to me unless they wish to infer that the separation of these dysfunctional bleeders on the basis of the endometrial picture is a rather artificial one. These data suggest to me that the defect responsible for the abnormal bleeding in these patients is not a constant one and that failure of ovulation must frequently occur in this group.

The fact that the cure rate following curettage in management of all types of dysfunctional bleeding taken together is from 25 to 50 per cent (Hoffman and others), figures which coincide rather closely with those given by the authors, further suggests that the division of patients purely on the basis of endometrial pattern may be artificial.

While all this may be true, however, without attempts such as these to elucidate the mechanisms concerned, our woeful ignorance concerning the cause and management of dysfunctional uterine bleeding is likely to continue.

The amazingly high incidence of associated medical disease seems to be almost certainly significant and to demand further investigation.

For the present the remarks of Arthur Sutherland in his paper on the histology of the endometrium in dysfunctional uterine bleeding still seem most appropriate: "It [is] finally apparent that almost any type of abnormal uterine bleeding can occur from any type of endometrium and that any attempt at diagnosis of functional bleeding without histological examination of the endometrium is quite unjustifiable."

DR. CARL G. HARTMAN, Raritan, N. J.—Some of you will recall that I gave a couple of lectures here when I was a young man approaching sixty, and they could not have been too bad because at the same meeting you elected me an Honorary Member.

The paper that has just been read involves a tremendous amount of work. Any of you who have tried to analyze curettings can appreciate that.

I have never seen anything like this in a monkey. The only pathologic bleeding that I have seen in a monkey is from an atrophic uterus. Doubtless you have seen that, too. This bleeding is very light, and in fact continues for months. Monkeys usually recover from it spontaneously.

Pathologic bleeding should be studied from the standpoint of the clotting mechanism. I have discussed this matter with my colleague, Dr. Singer, who is right in the midst of intensive research on the clotting mechanism.

There is a certain amount of irregular shedding of the endometrium normally; that is to say, there may be a shedding at one point, and the adjoining part will be perfectly normal.

Menstruation actually occupies a time period of only from ten to thirty seconds in any one spiral artery. I have seen this, and it is a thrilling sight to see actual menstruation take place.

Menstrual blood does not clot, but any flow that comes afterward does clot. Thus, for example, I have seen this in transplants in the anterior chamber of the eye by Dr. Markee, who worked in our laboratory for a year. He had eight or ten monkeys there continuously with transplants of the eye. This technique, by the way, he learned from one of your former members, Dr. Schochet. Dr. Markee worked for him when he was a student at the University of Chicago.

If you watch these transplants you can see by proper illumination the spiral arteries, just as you can see in the skin, with proper illumination, the tufts of capillaries; and you can watch them and see that a particular spiral artery will constrict and there will be a blanching area around it, then necrosis. Then you watch very carefully and you see the squirt of blood from this particular artery.

On one occasion Dr. Markee called me, and I rushed in and scared the monkey, and there was another gush of blood from the spiral artery. With the first gush the blood was not coagulated, and you could see the red blood cells drop to the bottom of the anterior chamber, where they flushed out and disappeared within a few hours. The next gush, however, which was due to my scaring the monkey, clotted instantly, and for several days that clot hung from the point of exit.

DR. SINYKIN (Closing).—The normal endocrine endometrial relationships have been pretty well defined, but the abnormal bleeding relationship is still quite vague. I certainly agree that much more work of a fundamental nature is needed before the mechanisms involved are clarified.

The problem as to why curettage remedies between one third and one half of the patients remains undetermined. It is quite possible and quite likely, however, that this is due to the removal of retained endometrium from the previous cycle, including the thickened spiral arterioles. This, however, does not explain why the retention of this tissue occurs initially.

Dr. Peckham makes the statement that break-through bleeding can have occurred in only about 20 per cent of the patients, because only in this number was the cycle shortened. I must disagree, however, that it is necessary for the cycle to be shortened with break-through bleeding, except with the initial cycle when break-through bleeding occurs. If break-through bleeding occurs regularly, two days before the usual expected time for menstruation, then that pattern will be set for each month, and the whole cycle would be just as long as previously.

We have not attempted to use progesterone therapy because we have not felt that it has the valid indication in view of the fact that the corpus luteum is functioning and apparently is producing a normal amount of progesterone; so there is no rational reason to use it. Stilbestrol has been valuable in our hands.

PERINATAL HYPOXIA CAUSED BY OBSTETRICAL ANALGESIA AND ITS AVOIDANCE BY THE USE OF PRODINE*

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THE practice of obstetrics has as its goal the delivery of a living and healthy baby to a surviving, healthy mother who has participated in the process with the maximum of comfort consistent with the safety of all concerned. Childbirth is much safer now for infants, and most of the former causes of perinatal death have been eliminated or reduced. At the present time about 40 per cent of the stillbirths and neonatal deaths are due to two major causes: anoxia and abnormal pulmonary ventilation. The cause of another 25 per cent of perinatal deaths is listed as "unknown" but many of these involve the respiratory mechanism. Thus it would appear that our efforts to lower still further the perinatal death rate, and that probably includes also the tragic mental and nervous cripples who survive, should be directed toward fetal and infant oxygenation. This involves not only providing adequate oxygen levels in the fetal circulation, but delivering a baby whose breathing and oxygen exchange apparatus is able to function completely on its own immediately after birth. According to the Bundesen report, of all the babies in Chicago who died in the first 7 days of life, from 1951 through 1954, 65 per cent died of respiratory distress and anoxia.

This paper does not deal with such things as separation, infarction, fibrosis, and senescence of the placenta, or with accidents to the umbilical cord, or with interference with fetal oxygenation from tetanic, tumultuous, or prolonged uterine contractions, or with collapse of the maternal blood pressure or reduction of the maternal blood oxygen level. It deals with the effect of drugs given to the mother during labor on the infant respiratory mechanism. As stated by Gibberd,³ "In asphyxia neonatorum we have to deal with a condition in which the medulla fails to initiate the necessary vigorous respiratory impulses, because its sensitivity is reduced."

The reactivity of the human body to any drug is variable. No doctor would feel safe in giving an old, debilitated individual the same dosage of a respiratory depressant as he would give to a healthy young man. Yet obstetricians unhesitatingly give the fetus powerful drugs, whose dosage is measured only by the discomfort of the mother. These drugs are administered to the fetus intravenously through the placenta. In a recent review Apgar and Papper¹ found that in the newly born infant the concentration of meperidine (Demerol) was between 60 and 70 per cent of the maternal concentration; for Pentothal sodium the fetal level in 7 to 12 minutes was about 50 per cent of the maternal level;

*Presented at the Twenty-third Annual Meeting of the Central Association of Obstetricians and Gynecologists, Columbus, Ohio, Oct. 6, 7, and 8, 1955.

for paraldehyde the distribution in the infant was equal to that of the mother; the concentration of nitrous oxide was about 60 per cent. Many years ago Smith and Barker¹⁰ showed that ether passed across the placenta but with a wide variation in percentage; they did, however, find a direct correlation between the blood levels of ether in the newborn and the degree of depression of the infant's respiration.

McCall and Taylor⁹ found that barbiturates, especially when given intravenously, depressed the oxygen metabolism of the brain, producing a significant lowering of cerebral blood flow. It must be remembered that the fetus is receiving its barbiturate from the mother intravenously in much the same way. That the brains of infants are affected by barbiturates given to the mother was shown by electroencephalographic studies by Hughes, Ehemann, and Brown,⁵ who found striking cortical depression in 20 newborn infants whose mothers had received Seconal in various doses.

Other evidence that the respiratory mechanism of the infant is impaired by drugs given to the mother during labor is found in the length of time required for the baby to gasp and to cry. Eckenoff, Hoffman, and Dripps² gave normorphine to infants to counteract the effects of Demerol given to the mother during labor. They found that if the mothers had 200 mg. of Demerol and 200 to 300 mg. of Seconal, the use of the narcotic antagonist in the child exactly halved the length of time required to establish a good cry. This demonstrates by a therapeutic test that giving a parturient woman meperidine and a barbiturate during labor produces a respiratory depression in her infant.

Taylor, Govan, and Scott¹² studied the length of time needed by infants to raise the capillary blood oxygen level from the fetal normal of 50 per cent to the infant normal of 91 to 98 per cent. All mothers received 100 mg. of Demerol and 0.5 mg. of hyoscine from 1 to 3 hours before birth. One hour after birth 45 per cent of the infants delivered under regional block anesthesia had achieved 90 per cent oxygenation, whereas only 15 to 20 per cent of the infants delivered with ether, gas, or Pentothal sodium had reached this level. It was noted that even at the end of three hours several infants whose mothers had received open drop ether for 5 to 12 minutes had failed to achieve 90 per cent saturation. While the experiment demonstrated primarily the additional depressant effect on respiratory exchange of inhalation anesthesia and meperidine-barbiturate analgesia, it gave an actual measure of the degree to which the tissues of the child were deprived of oxygen. It showed further the wide variation in response of the infants to essentially the same treatment given the mothers. We know that immature infants and premature infants must be protected against maternal analgesia and anesthesia. What safeguards can we set up to protect the mature infant who happens to be particularly sensitive to drugs or is in jeopardy during the second stage from placental or cord accidents?

One school of thought teaches to do away as much as possible with analgesics and anesthetics, and in order to assist the woman in her pain, advocates psychological preparation to minimize the nervous tension that accompanies labor. There are numerous psychological approaches to "natural childbirth" involving calm reassurance, or exercises in relaxation, or holding out the promise of posi-

tive ecstasy, or even frank hypnotism. The technique appeals to women for a variety of reasons. One must never underestimate the intuitive powers of a woman, however, and it may well be that the popularity of natural childbirth stems *partly* from an unconscious knowledge by women that analgesic drugs offer a risk to the baby. Certainly all of us have had some women plead or insist that they not be "knocked out cold" and state they fear the effects of drugs on the baby. This paper is not concerned with the merit or criticism of natural childbirth, but rather presents a compromise between it and the widely used meperidine-barbiturate analgesic combination.

The drug used was alpha-prodine hydrochloride, a narcotic sold under the trade name of "Nisentil." The material was purchased and not supplied, and was employed in 402 cases of labor under personal observation. The most striking effect noted was that it produced euphoria rather than narcosis in the mother. Whether the infant enjoyed any degree of euphoria could not be determined, but the absence of infant respiratory depression was amazing.

This might well be expected from the experimental work of Hurlbut and Dille⁶ who studied the respiratory rate of rabbit fetuses within the uterus and found that 3 mg. of prodine per kilogram of body weight administered to the mother rabbit produced very little effect on the fetus. On the other hand 5 mg. per kilogram did depress the respiratory rate to a degree requiring 3 to 4 hours to return to normal. They observed that the respiratory rate of the mother mirrored that of the fetuses and hence could be used as an index of the effect of prodine on the fetal respiratory rate. Translated to human beings this means that to a woman who weighs 110 pounds a dose of 250 mg., or to a woman of 150 pounds a dose of 350 mg. for any 4 hour period was absolutely safe for the fetus.

In the series being reported the largest amount of prodine given was 360 mg. in divided doses over a 16 hour period, and a total of 120 mg. in divided doses for any 6 hour period. Thus the effective dose, in women who responded to prodine, was less than one-third of the dosage which experimentally produced even transient respiratory slowing in the fetus. The maternal respiratory rates were recorded or merely observed in about 200 of the cases, and the only change noted was a slowing to normal in women who had been apprehensive. Only once was there an untoward side effect: an extremely anxious woman had a convulsion lasting 3 minutes immediately after a dose of 60 mg. This was not eclampsia. Three hours later she was given another 30 mg. of the drug without any reaction and 2½ hours later delivered a healthy baby under gas-oxygen anesthesia.

A large body of literature has now grown up on the use of Nisentil in obstetrics, almost all of it highly enthusiastic. Papers by Smith and Nagyfy,¹¹ Hapke and Barnes,⁴ LaForge,⁸ and Kane⁷ report careful observations. The percentage of "success" has varied with the dosages used and the interpretation of the individual observers, but all are agreed on the advantage the drug offers in the way of safety for the infant.

This can be confirmed in that of the 5 perinatal deaths in this series, not one could be attributed to the drug. The causes of death were: complete abruptio placentae, prolapsed cord, postmature child, erythroblastosis, and prematurity at 26 weeks. There were two cases of apnea, in one of which the mother had received intravenous meperidine given for a tumultuous labor by an excited intern, and one of unknown cause in which the mother had received a total of 90 mg. prodine in 7 hours and had been delivered under gas-oxygen-ether anesthesia by midforceps; the umbilical cord in this case was thin and almost atrophic, with no pulsation. Both infants survived and appear to be

perfectly normal 7 months and 2 years later, respectively. Only 26 infants could be said to have offered even the slightest resistance to immediate crying, the longest being $2\frac{1}{2}$ minutes. All of these had been delivered under gas-oxygen-ether anesthesia. The resuscitation of the other 369 infants (including two sets of twins) can be specified as immediate, meaning within 30 seconds. Since we have been using low spinal anesthesia none of the infants has failed to respond within that time interval.

While the prime advantage of prodine is its safety to both the mother and the infant, it has two other attributes to recommend it. The first is the fact that the women were conscious but euphoric. They could time and describe their contractions, ask for and use a bedpan, give the all-important warning that the bowels feel like moving, and lift themselves onto the cart and onto the delivery table. They could use supplementary inhalations of trichlorethylene if necessary. They could talk rationally, and almost never cried out even toward the end of dilatation. They acted and could be handled and treated exactly like individuals in the jocose stage of alcoholic intoxication. While smiling they reported having a really terrible pain and went right on talking; examination at the moment often revealed a powerful contraction which under meperidine-barbiturate unconsciousness would have made the woman scream.

If divided doses of from 0.5 mg. to 0.75 mg. of scopolamine were used to supplement (and at the request of the anesthetists, almost every patient received at least 0.25 mg.) there was considerable amnesia in addition to euphoria. *No barbiturate was used in any of these patients.* and most of them were fully conscious within ten minutes after the anesthesia was stopped. About half of them were allowed, with assistance, of course, to hold the baby as the cart was moved down the corridor or down the elevator to where they were greeted by their husbands. Thus the family group psychology, which is claimed as an important benefit of natural childbirth, could be enjoyed by these patients.

The second attribute is its flexibility. Many different dosage schedules were tried, some with and some without scopolamine in the beginning. Specific protocols are not presented herewith, not only to save time and space, but because of the tremendous variation in patients' reaction to pain and in their response to drugs, and the differences in length of labor, degree of dilatation when first seen, and the time when anesthesia was begun. Statistics are useless without means of accurate measurement, and an obstetrician's report on a drug must of necessity be his subjective impression of its effectiveness.

The dosage schedule found most satisfactory was an initial subcutaneous injection, when needed, of either 30 mg. or 60 mg., depending on the mother's weight, her degree of apprehension, the character and intensity of the contractions, and the estimate of the length of further labor. From then on doses of 30 mg. were given every 1 to 3 hours depending on the patient's response. This varied tremendously, but after the second injection it became apparent in some cases that some other technique would have to be employed if the woman were to be kept comfortable. In only 18 cases was the drug considered totally and completely inadequate, and it is possible that these women should have been given larger doses.

The principal shortcoming was its relative ineffectiveness toward the end of the first stage. This period varied from not at all in better than half of the patients to about 90 minutes in others, such as primiparas with posterior positions. Only one breech presentation fell into this group, but 14 others did very well with the drug. In about 20 per cent of the cases trichlorethylene inhalations were used to supplement the prodine, and in about one-third of these intermittent gas-oxygen was given with each contraction till dilatation was accomplished and the head was low enough for complete anesthesia and forceps delivery. More recently low spinal anesthesia has been used in such cases a little earlier than it would ordinarily have been administered.

Summary

1. Anoxia and abnormal pulmonary ventilation account for at least 40 per cent of perinatal deaths, and hypoxia is indicted for some of the tragic cerebral conditions of surviving infants.

2. Attention during labor must be directed not only toward the oxygen supply of the fetus but to the integrity of the respiratory mechanism that will shortly be required to supply the infant's tissues with oxygen from the air.

3. There is ample evidence that analgesics and anesthetics pass through the placenta and are thus introduced into the fetus intravenously. All these drugs produce some degree of depression of the respiratory center of the infant at the moment of birth, reflected in some degree of apnea and some retardation of tissue oxygenation in the first hour of life.

4. While most term babies can tolerate profound respiratory depression, a few cannot, and further reduction in perinatal mortality requires, for the sake of these few, a cautious use of narcotics and barbiturates.

5. One of the reasons for the popularity of natural childbirth may be an intuitive or unconscious knowledge on the part of women of the dangers to the infant of respiratory depressant drugs given to them to relieve pain.

6. Many of the advantages of natural childbirth can be obtained during the first stage of labor by the use of alpha-prodine hydrochloride (Nisentil), with or without scopolamine, but without barbiturates.

7. Observations are reported on a series of 402 term labors with divided doses totaling from 120 to 360 mg. The mothers experienced euphoria rather than narcosis, and were conscious and cooperative throughout labor.

8. In 4.5 per cent of cases it proved entirely ineffective. In about one-third of the rest supplementation with intermittent gas or trichlorethylene became necessary at the end of the first stage of labor and in the early second stage. Possibly larger doses should have been used.

9. Prodine proved completely safe for the infants who, despite terminal inhalation anesthesia, exhibited a remarkably low incidence of apnea and delayed respiration.

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Discussion

DR. LEO J. HARTNETT, St. Louis, Mo.—Since this essay deals with the use of analgesics during labor, we can eliminate from our discussion all the other causes of perinatal

death which might be avoided, except wherein there is a combination of factors which might include the use of analgesics. When one encounters results such as appear in this presentation, one must conclude that the drug is safe and it has been effective under the author's direction. My experience with this drug has been limited, and my only personal observations of any values are that it is more effective with multiparas.

There are several considerations which I believe might be given thought in a paper of this type, and the first of these is the observation that response to a drug will vary with the individual, occasionally over wide margins; therefore, the dosage must be based somewhat upon the effect desired and that which is obtained. This, of course, admits of limitations, and there is no animal experimentation that is likely to give a reliable answer. In the instances wherein the desired effect was not obtained by Dr. King, he attributed it to the inadequate dosage, and suggested the possibility that these patients might have been given larger doses. In my experience, one occasionally encounters patients who are completely refractive to the action of certain drugs, and perhaps some of these were represented. It was brought out also that the greatest shortcoming of "Nisentil" was its apparent ineffectiveness at the beginning of the second stage of labor, and it is at this point that almost all analgesics break down in their effectiveness. This breakdown requires the use of inhalation anesthesia of some sort, or the use of a regional anesthetic.

Inhalation anesthetic combined with an analgesic brings about a new combination of drug action, which will vary again with the individual patient, and the baby as well. It is the use, and often the abuse, both in choice of, and the administration of, inhalation anesthetics that can bring about the respiratory depression in the newborn. Personally, I regret that Dr. King did not employ either a spinal anesthetic or a pudendal block for his entire series. It would be my opinion that the greatest success could be attained with the use of prodine combined with the latter type of anesthesia. There seems to be little chance, however, that his results could have been improved.

In summing up I would like to refer to the author's statement which I quote:

"Many different dosage schedules were tried, some with and some without scopolamine in the beginning. . . . [Such] statistics are useless without means of accurate measurement, and an obstetrician's report on a drug must of necessity be his subjective impression of its effectiveness."

DR. HARRY M. KIRSCHBAUM, Detroit, Mich.—I want to mention Snyder's work on intrauterine fetal respiration, wherein he proved that there was intrauterine fetal respiration in the rabbit. He proved also that spinal anesthesia or cutting the spinal cord in a rabbit did not produce any change in the fetal respiration. Also, scopolamine is the only single drug that did not produce intrauterine fetal respiration in the cat. Therefore, it is the safest single drug. I have pictures taken in 1932 that show the prematures breathing immediately on straight scopolamine or straight spinal anesthesia.

I disagree that the spinal anesthetic induces depression in the premature.

DR. KING (Closing).—The element in prodine that impressed me most was its flexibility. For the obstetrician who has a fixed routine and who tells the nurse to go ahead and follow the standing orders and call him when the head is on the perineum, I do not believe prodine is the drug of choice.

For the obstetrician who likes to give what is needed and no more, who likes to provide the individual patient with the best drug for that particular case of labor, I feel it is almost ideal because of its flexibility.

The safety of the drug permits you to give 30 mg. every hour if necessary, or withhold it.

The use of scopolamine was at the request primarily of the anesthetist, because we were using inhalation anesthesia in the early part of this work. Within the last six months we have finally developed a low spinal anesthesia service, and the suggestion of Dr. Hartnett has been followed out in advance. We are combining prodine with low spinal, with superb results.

THE RELATIONSHIP OF THYROID FUNCTION TO ENDOMETRIAL HYPERPLASIA AND ENDOMETRIAL CARCINOMA*

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WITH THE TECHNICAL ASSISTANCE OF JOYCE WAGNER

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University School of Medicine)

A RELATIONSHIP between tumor growth and the endocrine glands has long been observed. Much of this work has been with experimental animals. Until recent years methods of assaying the functional activity of the human endocrine glands have been crude. The serum precipitable iodine determination, as a practical research method, is now available for precise evaluation of human thyroid function since it measures the amount of circulating thyroid hormone. Endometrial hyperplasia and endometrial carcinoma have been associated with each other and with disturbed endocrine function.^{1, 2} This study was designed to compare serum precipitable iodine determinations of patients with endometrial hyperplasia and endometrial carcinoma with those of a control group.

Clinically, hypothyroidism as well as hyperthyroidism is associated with every degree of menstrual disturbance from amenorrhea to menometrorrhagia.³⁻⁶ This certainly does not seem unreasonable in view of Gillman and Gilbert's⁷ study of ten thyroidectomized baboons. They noted disturbances of menstrual rhythm in all ten. The complex and variable reactions of the endometrium, perineal skin, and ovaries were felt to be a consequence of a widespread metabolic disturbance involving not only a modified gonadotropic activity but also a modified responsiveness of the ovaries to the pituitary hormone. On the other hand, Goldsmith and associates⁸ noted that a characteristic feature of 7 of 10 myxedematous women was ovulatory failure with a continuous estrogenic effect on the endometrium leading to the syndrome of metropathia hemorrhagica. All of these patients resumed normal ovulatory menses after therapy.

Hertig and his associates⁹⁻¹¹ report that women with benign cystic endometrial hyperplasia prior to the menopause are ten times as likely to develop endometrial carcinoma as women without this condition and those with atypical hyperplasia in the majority of instances later develop carcinoma.

The effects of varying the amount of endogenous and exogenous thyroid hormone on tumor growth in humans and experimental animals has been the subject of much study and speculation. Hertig and co-workers found that many patients with endometrial carcinoma have an associated endocrine disturbance—diabetes, two to three times the normal incidence; and thyroid disease in 3.1 per cent.

*Presented at the Twenty-third Annual Meeting of the Central Association of Obstetricians and Gynecologists, Columbus, Ohio, Oct. 6, 7, and 8, 1955.

Loeser² in an uncontrolled study suggests that the thyroid hormone is effective as a prophylactic agent against recurrence of genital cancer in euthyroid patients. Bather and Franks¹² have shown that dibenzanthracene-induced tumors in mice are less frequently produced if thyroxine is simultaneously administered. The rate of disappearance of the carcinogen from the tissues is increased.

Thus, because of the different possible associations of thyroid function and endometrial activity we felt that a controlled study in the human was in order. Furthermore, since the serum precipitable iodine (SPI) measures thyroid function directly and since the basal metabolic rate measures its function only indirectly and is subject to many errors, we felt that valid data could be obtained only by using this precise technique.

Methods and Materials

The SPI was determined by the digestion-distillation technique as modified by Danowski and associates.¹³ All determinations are carried out in duplicate on 3 ml. aliquots of serum. In our hands duplicate determinations almost always check within 0.5 gamma; if not, a third determination is made.

Our control series is composed of determinations on 117 individuals without suspected thyroid disease. A few of these were healthy employees, although the majority were hospitalized patients who were not critically ill and represented a good cross section of the population. In this control series, 91 per cent had an SPI between 3.5 and 7.0 gamma per 100 c.c. of blood; the mean was 5.1 gamma per cent. For convenience and because the normal distribution curve is slightly skewed, this is considered our normal range (i.e., 3.7-7.0). It is better expressed this way than in terms of standard deviation. (None of the controls had an SPI below 2.8 nor above 8.0 gamma per cent.) Only 4 per cent fell below 3.5 gamma per cent and 4 per cent above 7.0 gamma per cent.

It is well known that there exists excellent correlation between SPI and thyroid function; it is low in hypothyroidism and elevated in hyperthyroidism. The SPI falls when thyroid activity is decreased by thyroidectomy, by anti-thyroid drugs or by radioiodine, and it rises when thyroid substance is administered. We have yet to observe a patient with hypothyroidism, either primary or secondary, who has not had an SPI below 3.5 gamma per cent. The same observation has been made by Peters,¹⁴ and by Winkler.¹⁵

Furthermore, unlike the basal metabolic rate which is influenced by many factors other than the supply of thyroid hormone, the SPI remains remarkably constant from time to time in the same individual. Fluctuations greater than 1.0 meg. are unusual. Perlmutter and Riggs¹⁶ have found no difference in puberty and senescence in males and females. The SPI increases in normal pregnancy (range 6.0 to 11.0 meg.). In men and nonpregnant women one of us (W. W. E.) has shown that the administration of large amounts of estrogen causes a rise in the SPI followed promptly by a fall when medication is discontinued.¹⁷

It is known that the SPI may be elevated by any of the iodine-containing drugs used in roentgenography (Priodax, Lipiodol, etc.). These are chemical artifacts. However, no patient was included in this study who had iodides administered in such form or at such times as to complicate the SPI.

In all cases the diagnosis of endometrial hyperplasia or carcinoma was proved by endometrial biopsy, curettage, or hysterectomy. In most instances blood for the SPI was drawn prior to operation but in some the determination was made a few hours and, in a few, several days after operation. A surgical procedure even of considerable magnitude will not affect the SPI.¹⁸

Results

Endometrial Hyperplasia (Fig. 1).—In general, circulating thyroid hormone is normal in most cases of endometrial hyperplasia. Of 37 patients, however, 3 and possibly 2 additional patients had abnormally low concentrations of SPI. Thus perhaps 10 per cent of all cases of hyperplasia are found to be associated with true hypothyroidism.

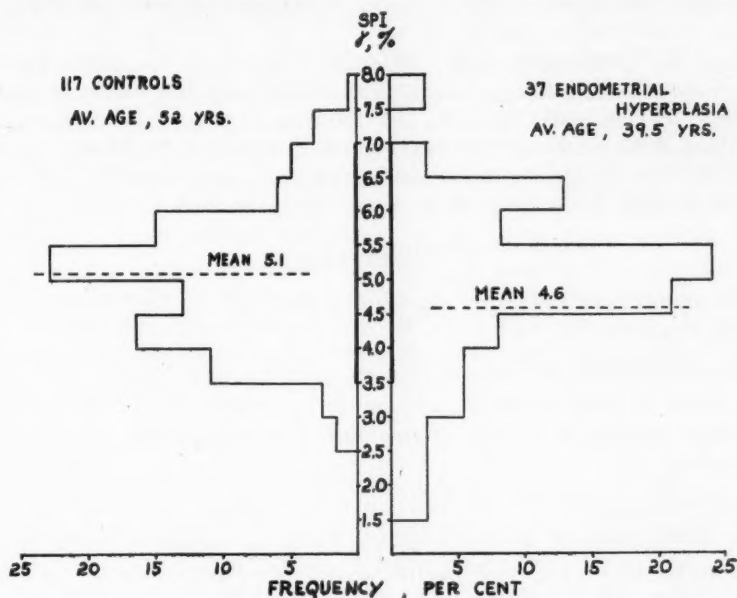


Fig. 1.

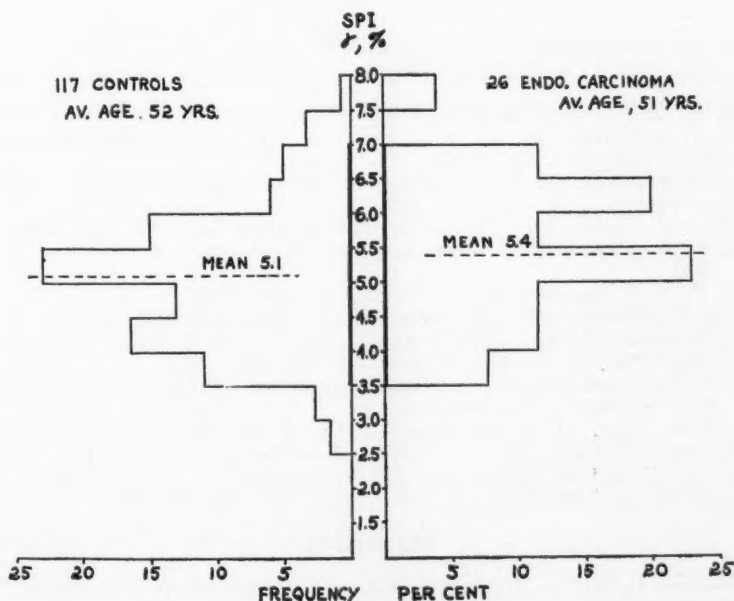


Fig. 2.

In these cases of hypothyroidism, the endometrial pattern and gynecologic symptoms were indistinguishable from those seen in patients without thyroid

disease. It may be that subjects with normal thyroid function have an endometrium which is less sensitive to normal concentration of thyroid hormone. On the other hand, we have no proof of this and other factors may be operative to produce a similar clinical picture and histologic pattern.

We feel that the low SPI in the 3 cases, however, and possibly in 2 additional cases, is significant and indicates hypothyroidism because only mercury (and that only for about 24 hours) and extreme malnutrition and hypoalbuminemia will lower the SPI. None of these patients received mercurial diuretics and none was critically ill.

Endometrial Carcinoma and Controls (Fig. 2).—The SPI in endometrial carcinoma falls entirely within the normal range and the mean is insignificantly different than in the controls (i.e., 0.3 gamma higher). It is interesting that not one patient with endometrial carcinoma was found to have hypothyroidism. We would have expected two or three cases if endometrial hyperplasia and carcinoma were similarly related to disturbed thyroid function.

Conclusions

1. Hypothyroidism does not commonly accompany endometrial hyperplasia or endometrial carcinoma.

2. From this study we are unable to support any theory that hypothyroid states may lead to endometrial carcinoma. A low but definite incidence of hypothyroidism (perhaps about 10 per cent) is associated with hyperplasia of the endometrium.

3. If administration of thyroid hormone exerts an inhibitory action on endometrial carcinoma or corrects many cases of endometrial hyperplasia, as has been claimed by some, the favorable effects are not due to correction of underlying hypothyroidism.

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Discussion

DR. ARTHUR B. HUNT, Rochester, Minn.—One can concur with the authors that the protein-bound iodine test is a very accurate one with which to gauge thyroid function. However, Blackburn,¹ working on metabolic disease at the Mayo Clinic, has observed definite exceptions in a small percentage of cases in the accuracy of this test not only in myxedema

but also in the hyperthyroidism of Graves' disease and that associated with nodular goiter. This observation, together with the fact that the series of cases of hyperplasia of the endometrium and cancer of the endometrium presented were necessarily small, could well mean that the incidence of hypothyroidism, perhaps of about 10 per cent associated with hyperplasia of the endometrium, may not be significant. Blackburn's data on the 4 cases of myxedema may make the authors' final conclusion partially untenable since they show that desiccated thyroid may correct myxedema even though the initial protein-bound iodine tests are within normal limits. The response of hyperplasia or cancer of the endometrium to thyroid treatment, however, is another matter.

Statisticians can show many sound reasons why the comparison of two disease states in even a large group of patients can be precarious from their viewpoint. Nevertheless, in the last five years (1950 through 1954) there were 1,560 patients with various myxedematous states diagnosed at the Mayo Clinic. Among these patients there were 12 with cancer of the cervix, or 0.8 per cent, 6 with cancer of the corpus of the uterus, or 0.4 per cent, and 27, or 1.7 per cent, with cancer of the breast. It is difficult to state what these statistics suggest but it appears unlikely that hypothyroidism and cancer of the uterus have a striking coexistence.

The above scanty information that I can bring to bear on this problem supports the negative results reported by Dr. Stoddard and his associates in this excellent study. It may be they have not entirely settled this question but the longer one reads the literature of a specialty the more does one appreciate the fact that clear-cut findings of a negative nature are as valuable as a report presenting positive findings.

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DR. STODDARD (Closing).—I think those 4 cases of myxedema with normal, or at least with not depressed, protein-bound iodine determinations should be reported if they have not already been, in view of the fact that Peters and Winkler, and also Engstrom, one of the co-authors, who have had a wide experience with hypothyroidism in myxedema, have not encountered any cases of myxedema with SPI determinations that have been above 3.5 gamma per cent.

I think that, when any of us run across any unusual cases of this sort, specimens of blood should be sent around to other laboratories for running of accurate determinations, to try to see whether perhaps there is a deficiency of the method or whether they are true exceptions to the rule.

PROBLEMS OF MATERNAL DEATH STUDIES—SOME RECOMMENDATIONS FOR THEIR SOLUTION*

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THE importance of maternal death studies no longer need be argued. Their value in reducing maternal mortality by locating and specifying shortcomings in obstetric practice has been demonstrated repeatedly. Likewise, the part they have played in shaping educational programs and in the establishment of standards and regulations is well known. As these studies have increased in number, however—they now are virtually national in extent—many problems related directly to the studies themselves have arisen. Some are of such magnitude that the practical application of the lessons which they can teach is denied them.

Published reports on maternal mortality show marked variations in policy and function among these committees. They reveal significant differences in terminology as well as in collection, interpretation, and utilization of the data. The Special Committee for the Study of Maternal Deaths of the Central Association of Obstetricians and Gynecologists was formed, with the authors as cochairmen, to examine these and associated problems. It was asked to determine whether a mutually acceptable approach toward them could be found. To obtain information which would permit valid conclusions, members of the association were asked to serve as subcommittee chairmen and were arbitrarily assigned specific problems for investigation. They were asked to organize their own subcommittees and to include, whenever feasible, representatives from their state maternal welfare committee, their state health department, as well as others known to be interested. It also was suggested that representatives from state and local obstetric societies and general practice groups be invited to serve.

This report presents some of the conclusions and recommendations of these investigations. Obviously the complete findings cannot be included. Of necessity this is selective and incomplete. The committee is drawing up its findings in detail for circulation among the local and state maternal welfare committees and interested individual physicians in the geographic area of the Central Association for critical study and comment. The committee has been in surprising agreement on basic issues. We believe, however, that wider consideration will demonstrate better those areas in which essential agreement can be expected. Such, too, will determine more thoroughly the extent of divergency and the nature of disagreements. Those cooperating in this critical review will be invited to present other problems which could be included in this

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study. Thus, we hope, those handicaps which lessen the effectiveness of maternal death studies will be emphasized and those in most urgent need of solution will be brought into sharper focus.

The American Committee on Maternal Welfare recently completed a survey of current policies and practices of maternal welfare committees.¹ This found that maternal mortality committees existed in 44 of the 48 states, "but that each was a pioneer and nothing was common to all."² In the area of the Central Association, in all but Tennessee, such committees are functioning on a state level. In addition, there are 16 active local committees, including one in Chattanooga, Tennessee. The American Committee formulated a suggested outline for organizing and operating a maternal mortality committee. These suggestions, however, do not consider, except in passing, those which we have investigated.

The American Committee suggests that the information concerning maternal deaths be obtained "1. From copy of death certificate (640-689) on all pregnancy complications or puerperium, 2. From others having information."³ Restriction of study material to the 640-689 section of the International Statistical Classification will omit many deaths which are of extreme importance, such as those due to heart disease and anesthesia. Data obtained wholly from the death certificate are notoriously unreliable. McKelvey and Freeman,⁴ reporting on the Minnesota study, found that during 1950 and 1951, on the basis of supplementary information, the cause of death as stated on the death certificate had to be changed in more than a fourth, 27.2 per cent. We have found many instances where the stated cause of death does not suggest even remotely that pregnancy was the real or significantly related cause. In one of our study cases death in an 18-year-old primigravida was certified as due to coronary occlusion when the actual cause was proved to be hemorrhage from a ruptured uterus. Many maternal deaths now being missed would be included if a simple addition to the death certificate requiring the date of the last pregnancy would be adopted.

Many studies gather their information by questionnaires sent to the attending physician. If adequate information is to be obtained, these must be carefully devised; that developed by the Wisconsin committee is exceptionally thorough. When questionnaires lack sufficient detail or are incompletely filled out, the cause of death and responsibility often cannot be determined. We believe that the data finally should be summarized in chronological order so that the course of events involved in the fatality may be more efficiently evaluated.

Better information results if it is collected by a trained obstetrician. Our study convinces us that precise and complete data are best obtained by combining the questionnaire and personal study methods. The results of this method as used in Wisconsin are adequate testimony.² We recommend that upon receipt of the notification of death the authorized study group send a questionnaire to the attending physician. When this is returned it is to be forwarded to the interviewer or consultant for study prior to his visit with

the physician. This gives important support and cooperation to the study. The attending physician, already harassed, is given the courtesy of reporting his data first. Subsequently he has the opportunity of discussing his problems with a specialist who is also familiar with them. Review of office records, autopsy protocols, and hospital records is more readily obtained.

It must be emphasized that the material recorded for study as well as the summary must be strictly factual. Should the committee desire the opinions of the interviewer, these should be prepared and forwarded separately from the collected data. Local considerations, including the type of community, may not always permit the study method recommended. Because of its obvious superiority, however, the combined method should be planned for and made a part of every survey as soon as feasible. The accuracy and completeness of the factual material available for study determine the validity of the conclusions of the committee.

The legal status of maternal death studies is a matter of considerable concern to many committees. Questions have been many. What protection is there for committee members and case data from legal action? Can the records be subpoenaed by a court? Can the opinions of the committee be introduced in actions against the attending physician? Should immunity regulations be enacted in the various states? A special subcommittee investigated this problem. As in many other fields of medical practice, legal precedent and opinion are scant. The Law Department of the American Medical Association informs us, in answer to questions presented to them, that they are conducting a study of the basic legal issues relating to maternal death and other similar studies undertaken for the purpose of improving general health and advancing medical science. When completed, their study will be published in *The Journal of the American Medical Association*.

Governmental health agencies are empowered to gather information to be used as vital statistics and for the preservation of public health and the prevention of disease. Vital statistics are collected for public use. Thus, the documents upon which these are based are considered to be public and can be received in evidence by a court. Data collected for the preservation of public health may, however, in the public interest be withheld upon the decision of the responsible official from general inspection and publication, unless otherwise specified by statute. The Minnesota legislature has recognized the altruistic aims of investigative studies by organized medical groups and in the spring of 1955 enacted a law which provides that the information obtained in such studies "shall not be admissible as evidence in any action of any kind in any court or before any tribunal, board, agency or person."

Studies which are voluntary and scientific in purpose rather than governmental and statistical must be conducted with particular prudence. In the collection and recording of information the rights of privacy must be respected. Complete anonymity must be maintained in all reports. In the absence of a specific law, the records could be subpoenaed by a court. The use which could be made of them, however, is uncertain. There is little law and

some difference of legal opinion on this point. The records might be submitted as factual data for evaluation by a judge or jury. They might be considered as hearsay and not be acceptable as evidence. If the information were gathered by an interviewer from records and if these records were previously admitted in evidence, the interviewer might be subpoenaed and be required to testify in this respect. But if his interpretation of the information were insisted upon, in the opinion of private legal counsel, he would become a recalcitrant witness and do more to damage the case than to sustain it. Legally this is considered foolhardy and is unlikely to occur. It is generally agreed in legal circles that it is disastrous to base a plaintiff's case on a recalcitrant expert witness.

It can be concluded that the legal status of maternal death studies still remains undetermined. It appears that the best legal protection for all types of studies is to be obtained from carefully conceived legislation, such as enacted in Minnesota. Without such immunity, investigations should be directed so that the material gathered is confined strictly to factual information. Summaries should never contain statements of opinion. Evaluation is the function of the committee itself. The conclusions which they reach upon anonymous records can be kept separate from the gathered material. These represent judgments made upon what can be considered as hypothetical material. Finally, in the event that an interviewer or consultant is summoned by a plaintiff's attorney to appear as an expert witness, the importance and value of appearing as a recalcitrant witness should be emphasized to him.

Our investigation into sponsorship of maternal mortality surveys makes us agree with the American Committee and others^{3, 5} that joint sponsorship by medical societies and health departments is most desirable. It is preferable that this be on a state level. Such sponsors impart an aura of authority to the study and open many doors. As has been pointed out, health departments have authority to collect statistics and examine records. As a joint sponsor their statisticians, experienced laboratory personnel, and artists become available to the study for consultation. Similarly, the public relations counsel and committee of the medical society can be invaluable in presenting the conclusions and recommendations of the committee in a manner acceptable to county societies, hospitals, and the public press.

To ensure against improper use of the materials of these studies, we recommend that all use be first approved by the executive committee of the medical society. Actual custody of the collected materials is best given to the governmental agency. It is able to provide proper storage facilities, continuity of personnel, as well as relative immunity to legal inquiry. Moreover, they are more capable of assuring the anonymity which these studies require.

In our opinion, the costs involved in these studies should be underwritten by the sponsoring agencies. Funds for this purpose are provided by the federal government under existing legislation. Other sources can be found if necessary. For efficient function we believe that the committee should be granted definite sums based upon a submitted budget. Compensation of inter-

viewers, travel and associated expenses of committee members, secretarial services, costs of publication and mailing, including reprints, appear to be justifiable expenses. Committee members contribute generously in time and effort and should not be expected to pay the costs of these studies from their pockets.

After the factual data have been gathered, and for anonymity given code numbers by the custodial agency, they should be reviewed by members of the committee. Our study concludes that this is most effectively accomplished by a small subcommittee of experienced obstetricians with rotating membership. A general practice representative may be included and often becomes a helpful member. Consultants from allied fields, such as cardiology, pathology, and anesthesiology, should also be included and called upon when appropriate cases are to be discussed. Case protocols should be prepared and distributed in advance of the review. Each case should be assigned to a member of the committee for his intensive study and report at the meeting. This review, we believe, should reach conclusions on five points: (1) cause of death, (2) preventability, (3) responsibility, (4) factors involved, (5) specific recommendations. These findings of the review committee have their greatest effectiveness when they are formulated into a letter and sent to the physician concerned. If it is believed that these should have prior acceptance by the entire committee, such a policy can be adopted. The letter sent should include the conclusions reached and outline the reasoning involved. As seems appropriate, it may be expansive and epitomize current concepts, or it may be critical and point out specific shortcomings. A digest of the findings sent to the administrator or department chief of the hospital has been found to be an extremely valuable aid in correcting deficiencies in facilities and organization. Because of the privileged nature of this material, identity of the individual physicians and hospitals should be given by the custodial agency to the secretary after the evaluation has been made as confidential information to be used only in preparing the letter from the committee.

Discussion of individual cases in open meetings is important for its educational value. These may be selected either prior to or following review by the evaluating committee. Formation of subcommittees for this purpose within local areas is urged. Regular publication of conclusions both as statistics and reports on specific problems enhances the stature of these studies and adds to current information on maternal mortality. The methods utilized will depend upon the abilities of the committee members and the sources of publication available to them. Reports of individual cases, in general, appear to be avoided but the committee wishes particularly to endorse these as an educational feature. The reports of the Massachusetts committee appearing regularly in the *New England Journal of Medicine* are models of this type of publication.

Proper definition of terms is crucial in these studies. Here words must be understandable and have consistent meaning. Our committee made definitions one of its major concerns. Only a few of the more important ones will be

presented. Some of our recommended definitions differ from those presently used. They present the point of view of the practicing physician who is not held by regulation to the uncritical acceptance of traditional language.

What is a maternal death? We believe that this term should include the deaths of all women who die during or following pregnancy, up to six months of the termination of the pregnancy. Studies of deaths related to pregnancy must be based upon essentially similar data. We believe that these must include the deaths of all women who were pregnant at the time of death or who died during the puerperal period when the adverse effects of pregnancy still may be factors in the death. The formal definition which we recommend is as follows: A maternal death is defined as the death of any woman dying of any cause whatsoever while pregnant or within six months of the termination of the pregnancy, regardless of the duration of the pregnancy at the time of termination or the method by which it was terminated (e.g., abortion, laparotomy for ectopic pregnancy, premature delivery). These deaths will give a gross figure; many may not be related to the pregnancy. Exclusion of the unrelated deaths permits the calculation of the actual mortality rate. Both for accuracy and evaluation, however, it is important that the basis of exclusion be specifically stated in the reports.

Maternal deaths or, as some prefer, deaths related to pregnancy, are divided in the International Statistical Classification into maternal and non-maternal. Since these are defined only by implication, there is considerable confusion regarding these terms. From our study the use of obstetric and nonobstetric seems preferable. Most important of the deaths related to pregnancy are those which involve purely obstetric factors, those which result directly from complications of pregnancy or from obstetric intervention. Thus a death due to obstetric causes would be defined as a death due to complications of the pregnancy itself or to intervention elected or required by the pregnancy or resulting from the chain of events initiated by the complication or the intervention. Here would be included deaths due to amniotic fluid embolism and anesthesia. The latter is a maternal death due to obstetric causes; obviously the fatal anesthetic would not have been given had the pregnancy not required an anesthetic.

The inclusion of nonobstetric deaths as maternal deaths may appear to be a contradiction in terms. Yet these are significantly related to pregnancy and are fundamentally problems of the obstetrician. Nonobstetric deaths, in our opinion, are deaths resulting from the adverse effect of pregnancy upon disease present before or developing during pregnancy. We would define nonobstetric deaths as deaths due to disease present before or developing during pregnancy, not a direct effect of the pregnancy, which was seriously aggravated by the physiologic effects of pregnancy and caused the death. Deaths due to heart disease as complicated by pregnancy would be included here.

How should maternal mortality rates be stated? The subcommittee investigating this problem concluded that as usually reported the maternal mortality rate is not a true statistical rate. The numerator, the number of deaths,

is specific. The denominator is arbitrary and does not include all women involved in the risks of pregnancy. Unless they are included the actual risk of pregnancy is overstated. Yet it is impossible at the present time to calculate this denominator. The most satisfactory alternative would be to use a figure which includes all reported births, both live births and stillbirths. Definitions of stillbirths vary among the states, however. Consequently, such a figure would be a variable and thus not valid in arithmetical computation. The National Office of Vital Statistics calculates maternal mortality in terms of live births alone, pointing out that fetal deaths are proportionally constant and their exclusion makes no significant differences in the calculated rates.

If live births are accepted as the denominator, of what order should it be? Maternal mortality was first reported in terms of 1,000 live births. As maternal deaths decline, however, their importance can be emphasized only in terms of larger numbers. The National Office of Vital Statistics now reports maternal deaths in terms of 10,000 live births. Rounding out the fractions when 1,000 live births is used produces important discrepancies. We recommend the universal adoption of 10,000 live births as the denominator so that maternal mortality rates may have statistical significance.

Our study found assignment of preventability and responsibility to be an exceptionally sensitive area in studies of maternal deaths. One of the committee members, presenting the negative attitude, stated, "Little is to be gained by publicly pointing the finger of responsibility for a maternal death at a specific factor. The professional man who requires that type of impetus to his self education could hardly be expected to respond to it." We cannot disagree. Unfortunately, the problem of reforming the individual sinner, professional or spiritual, probably never will be solved adequately. Nevertheless, and the member quoted agrees with us, we insist that these evaluations are both important and valuable. It is our conviction that the factors contributing to maternal deaths must be examined critically and that they must be assessed conscientiously in relation to the best possible standards of medical practice. Unless this is done, the problems concerned in obstetric care and in the management of the complications of pregnancy will not be discovered, properly appreciated, or adequately presented for solution.

Nonpreventable deaths obviously do not result from shortcomings in management. Such deaths represent medical helplessness and professional failure and teach us nothing. Actually such deaths are few. From available reports, preventability ranges from 35 to 85 per cent. This suggests a reluctance, perhaps a lack of courage, to evaluate maternal deaths in terms of current obstetric capability; or at least diverse criteria of preventability. Otherwise this variation must be assumed as reflecting vast differences in professional ability in the various parts of the country, a situation which to us seems quite impossible today.

In assigning preventability, some committees distinguish between the specialist and the general physician. This, we believe, is dangerous. Like any double standard it may provoke promiseuity. Moreover, it is an open admission that complete anonymity was not maintained. We admit that one

should expect more from the specialist than the general physician. This difference may be taken into consideration in the letter to the attending physician where the secretary can make more stringent and pointed comment to the specialist in the well-equipped hospital and be more generous to the general practitioner in less favorable surroundings.

To avoid the onus of judging the individual, preventability should be judged in an ideal, academic sense, one which to many might seem unrealistic. The concept of preventability we wish to present involves three assumptions. First, the physician possessed all the knowledge currently available relating to the factors involved in the death. Second, by experience he had reached a high level of technical ability. Third, he had available to him all the facilities present in a well-organized, properly equipped hospital. Under such assumptions, unless the patients were actually moribund when first seen by the physician, most maternal deaths could be judged as "probably" preventable. Assignment of physician responsibility emphasizes shortcomings in diagnoses, judgment, management, and technique. It should be so placed if the factual data indicate that the physician failed to recognize the complication or to evaluate it properly, if there was injudicious haste, delay, or timing of operative intervention, if he failed to utilize currently acceptable methods of treatment, if he were technically inept, and, finally, if these failures could have been averted by proper and timely consultation.

Patient responsibility should be recognized, but never as an excuse for professional inadequacy. It should be assigned when death results from a complication for which there is generally successful treatment but which the patient denied herself by delaying her initial visit to the physician, by delaying obtaining medical care after the symptoms were obvious at a layman's level, or, finally, by not following the advice and instructions of her physician.

Another aspect of professional preventability and responsibility concerns the hospital. This concept, relatively recent in acceptance, insists that in terms of modern obstetrics the hazards of delivery cannot be met successfully unless the hospital provides: (1) a separate, well-directed maternity section, (2) a blood bank, (3) competent 24 hour anesthesia service, (4) suitable 24 hour x-ray facilities, and (5) adequate 24 hour laboratory service. We believe that any hospital accepting obstetric patients should provide these facilities and personnel. Deaths from hemorrhage result principally because blood for transfusion is not available quickly enough or not in adequate amounts. They emphasize the importance of a constantly functioning laboratory and its adjunct blood bank. Without the latter, public awareness of the importance of blood transfusion in averting fatalities must become the joint effort of the physicians and hospital administrator so that an efficient, active donor list can be established and made to function. Maternal deaths attributed to anesthesia demonstrate inadequacies in the personnel administering these agents. We believe that in many of these instances the hospital should be held responsible because of the failure to provide adequately trained anesthetists to the obstetrician. We realize that at present many hospitals are unable to supply the facilities and personnel necessary for proper obstetric care.

Likewise we recognize that all physicians will not be thoroughly trained technicians and that all cannot be constantly abreast of the latest in obstetric knowledge.

If because of inadequate evidence a clear-cut decision cannot be made, yet shortcomings in care are apparent, we believe that it would be preferable to assess preventability as *undetermined*. An attempt should always be made to determine preventability and to locate the responsible factors. Our committee agrees that only by humble, honest self-criticism will we find what improvements are necessary if the aim of eliminating preventable maternal deaths is ever to be achieved.

Classification of the cause of maternal deaths has been a perplexing problem. The International Statistical Classification has been used in most studies, at least in their inception. Yet even public health biometricians do not consider this as entirely suitable.⁶ Some of its shortcomings have already been pointed out. If all deaths relating to pregnancy are to be classified, the distinction between obstetric and nonobstetric causes which we recommend should be made. From our investigation we propose that the usual titles be rearranged in some manner as follows:

CLASSIFICATION OF DEATHS RELATED TO PREGNANCY

- A. *Obstetric Causes*
 - 1. Hemorrhage
 - 2. Toxemia
 - 3. Infection
 - 4. Vascular accidents (air embolism, amniotic fluid embolism)
 - 5. Anesthesia
 - 6. Miscellaneous (molar pregnancy, transfusion hemolysis)
 - 7. Undetermined
- B. *Nonobstetric Causes*
 - 1. Cardiac disease
 - 2. Vascular disease (hypertensive vascular disease, vascular embolism)
 - 3. Reproductive tract disease (uterine and adnexal tumors)
 - 4. Urinary tract disease
 - 5. Hepatic disease
 - 6. Pulmonary disease
 - 7. Metabolic disease (diabetes)
 - 8. Miscellaneous (appendicitis, peritonitis)
- C. *Nonrelated Causes*
 - 1. Communicable and infectious disease
 - 2. Blood dyscrasias
 - 3. Malignancy
 - 4. Suicide
 - 5. Murder
 - 6. Accidental
 - 7. Other

Such classification will permit comparison of incidence and mortality in these conditions. If random or incomplete classifications are used, great care should be taken to specify clearly the kinds of complications included under each title.

The compression of this report, almost to the point of sterility, as well as its omissions is sincerely regretted. We shall be glad to send a copy of our detailed findings to all who request it. The entire committee has been gratified and impressed by the interest which the investigation has aroused. Upon invitation, the plan and objectives of the study were presented⁸ at the Joint Conference on Maternal Welfare sponsored last March by the Maternal and

Child Health Committee of the American Medical Association. At that meeting the need of a workshop type of conference on a national level became evident. We were encouraged to pursue our investigation. When our final conclusions are made they will be presented to The American Committee on Maternal Welfare and the Maternal and Child Health Committee for their consideration and, we hope, eventual guidance to those committees undertaking studies in maternal mortality.

Much still remains to be done. These preliminary recommendations need shaping and further direction. This must come from a free expression of opinion, both adverse and supporting. Now more than ever before, our committee believes this study is important and should be continued. Wider participation is needed. We are convinced that it is possible to arrive at definitions, procedures, and techniques which will be acceptable mutually and will be of practical value to those working in this field in their efforts to improve maternal care in the various communities throughout the nation.

We wish to acknowledge the invaluable assistance of the various subcommittee chairmen, Kenneth E. Cox of Kansas City, Missouri, John E. Faber of Rochester, Minnesota, Fred J. Hofmeister of Milwaukee, Wisconsin, Raymond J. Jennett of Phoenix, Arizona, Joseph Krebs of St. Louis, Missouri, Brooks Ranney of Yankton, South Dakota, and Palmer E. Sutton of Royal Oak, Michigan. Without the considerable time and critical thought they and their associates gave to their assignments this report could not have been written.

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3019 NORTH WOODWARD AVENUE

Discussion

DR. WILLIAM V. LUETKE, Madison, Wis.—For the past three years there has been a maternal mortality study in Wisconsin. We have little to add to the general problem, and our findings are not significantly different from those of other groups.

In 1953 there were 88,408 deliveries; in 1954 there were 91,570 deliveries. During the same years there were 66 and 61 deaths, respectively, for maternal death rates of 0.7 per 1,000 and 0.6 per 1,000. These rates, at first, approach the ideal until each death is studied and analyzed as to its preventability or unpreventability. I have only the complete 1953 study, and I want to mention only a few of our findings for that year. First, concerning preventability, 12 cases could be excluded because the deaths were in no way related to obstetrics. Then, judging "preventability" in the very ideal sense which, of course, is not fair to anyone concerned, 13 cases could be called "unpreventable" and 41 cases could be judged "preventable." If the preventable cases then had a second chance and 100 per cent success concerning the management was obtained, the maternal mortality rate would "ideally" be approximately 0.3 per 1,000 (*obstetrical utopia*).

Of the 41 cases that were judged preventable, 21 could be attributed to shortcomings of the doctor alone, in 9 more both patient and doctor were at fault, and in 3 more doctor and hospital were jointly deficient. The point I am making is that preventability was laid at the doctor's doorstep in 32 of the 41 cases.

The big killers were toxemias and hemorrhage; there were 22 cases of each. These are mentioned because again this is where such studies glaringly bring out medical mismanagement and deficiencies. There were 3 cases of renal toxemia. There were 8 cases of hypertensive toxemia. There were 11 cases of pre-eclamptic-eclamptic toxemia, four of these patients died from cerebrovascular accidents, 3 died from respiratory center paralyzes, 2 died from pulmonary emboli, 1 died from a uterine laceration, and 1 died in shock because of abruptio placentae. In the entire toxemia group there were 6 deaths that were attributed to hemorrhage.

Hemorrhage caused the death of 22 patients. One was a case of massive gastric hemorrhage from gastric ulcers and is, of course, excluded. Three patients died from intra-abdominal hemorrhage because of ectopic pregnancies all without benefit of surgery. There were 2 cases of afibrinogenemia, 2 cases of spontaneous rupture of old classical cesarean section scars, and 1 case of irreversible shock during a cesarean section and another with abruptio placentae. There were 10 cases for sure and quite obviously 2 more for a total of 12 deaths due to uterine laceration or rupture. Of these 12, there were 2 incidents of excessive stimulation with pituitary extract, 3 of manual dilatation of the cervix, 2 with version and extraction, the remaining 5 all had traumatic deliveries of one sort or another.

In summarizing the Wisconsin study, our findings were the same essentially as in previous studies: death certificates often in gross error; only 18 postmortem examinations made and only 2 of these in the preventable group; consultations infrequent and often by inadequate personnel; poor doctors' records; poor prenatal care; failure to recognize and treat critical situations; inadequate hospital staffs; failure to recognize the severity and rapidity in toxemias and failure to treat adequately; versions and extractions; excessive use of pituitary extracts; traumatic deliveries; failure to diagnose and treat lacerations of the uterus; patients with cardiac, renal, and hypertensive disease who should not have been pregnant and who should have had interruptions; inadequate use of blood; mismatched blood; lack of patient cooperation; patient ignorance; religious barriers. These cover most of the factors involved in these deaths.

We feel that the important thing concerning these maternal mortality studies, once the interviewing and analyzing have been done, is to take the findings back to the grass roots from where they came. The statistics were presented to hospital staffs, county medical societies, district medical meetings, the State Medical Society convention including separate presentations to the House of Delegates and the State Medical Society council. Eight separate papers were written in the State Medical Journal. The state was completely covered from north to south. Approximately 100 different presentations were given.

Showing the medical profession—very pointedly—the type and caliber of obstetrics as practiced by a few of their colleagues is the value of a maternal mortality study.

DR. PALMER E. SUTTON, Royal Oak, Mich.—At a meeting in Houston, Texas, Drs. Ott, Longyear, and I presented a paper asking, "Do Maternal Mortality Studies Have Value?" Apparently the continuation of effort indicates that most of the people who have considered this subject believe that these studies do have value.

Ultimately our aim is to reduce preventable deaths. I want to point out one item in order to indicate the tremendous responsibility that falls upon those who attempt to improve our rate of preventable deaths.

A generation ago a study was made in Michigan (and Michigan was nothing more than an example), and we found in the two and a half year period from 1926 to 1928 that there were 1,627 maternal deaths in the State of Michigan among 245,000-odd live births. In the generation since then, our recent survey points out that we had 510,000 live births in a three year period, 1950-1952, with 271 maternal deaths, as contrasted with the previous 1,627 deaths.

The medical profession has come a long way, and the responsibility of reducing maternal deaths from here on, I believe, is much more difficult than it has been in the past generation.

When you attempt to improve the maternal death rate at the state level you encounter a great deal of difficulty—shall I use the word “mechanism”?—and it seems to me we can do it only by a process of evolution and not revolution. I think our main weapon is education. It is important that we reach some uniformity at the national level.

If education be our goal, then we have two things to use. Communication is a mechanism of education. Therefore, published reports, with all of the ideas in regard to what has happened, seem to be important. We also believe that meetings at the local level are extremely important, and that in order to publish things and have meetings that have uniformity, the ideas that have been expressed here by Dr. Longyear must be considered and must receive acceptance.

COMMANDER HAROLD H. HILL, Bethesda, Md.—I have been very much impressed with Dr. Longyear's work, particularly because I have been interested in maternal welfare especially recently, and I think some of you might be interested in knowing that in the armed forces we are delivering something like 140,000 babies a year. In our naval hospitals we are delivering from 400 to 500 babies a month.

Surprising as it may seem, we do not have maternal welfare committee studies in progress, and I have been very much interested in instigating the formation of an Armed Forces Maternal Welfare Committee, whereby something similar to this fine work that Dr. Longyear and others have done can be instituted. I assure you that it is not an easy task.

We realize the tremendous responsibilities that we have, and we are cooperating with the American Committee on Maternal Welfare, of course, in getting this project under way. If we can just get the Army and the Air Force to go along with us, I think we will have something next year.

DR. LONGYEAR (Closing).—The Committee has recommended the adoption of the questionnaire as utilized in Wisconsin as a standard. We believe that by little additions of making dual contact we perhaps will secure more information.

The change in the death certificate, which Dr. Luetke has suggested, should be carried back to each state. If we can add just one thing—the date of the last pregnancy of the woman—we will pick up many deaths that we are missing now. Currently we have to resort to a system whereby we match all death certificates of women in the childbearing age and the birth certificates during that same time and, surprisingly enough, we pick up a fair number of maternal deaths that way.

Death certificates are prone to refer to the cause of death as heart failure, and disregard anything that may have led up to it or that may have been associated with it.

The thing we are trying to establish here is an avoidance of approval or disapproval when we talk about preventability. We have reached the point where we have brought maternal deaths to an extremely low figure, and we are looking for preventable factors, not necessarily preventable deaths. If we use the ideal academic sense of setting our standard as one of perfection, we can talk about the small things that add up to large things and that prevent deaths.

We find, too, that this is better received, because an individual does not mind nearly so much being held against the scale of perfection rather than against the ordinary standard of practice in his particular community.

We also found that the academic ideal was better received by the public. Recently in the Detroit area they published in the newspapers the report of the Maternal Mortality Committee, in which these things were charged very frankly. It was well received by both the profession and the public.

As Dr. Luetke suggested, we have utilized the information in such a manner that it can be carried out to the small groups. The University of Michigan's postgraduate lecture series which goes throughout the state has carried the Michigan series to the small groups, focusing somewhat upon the problems mentioned.

I would like to emphasize the point Dr. Luetke mentioned, the great number of ruptured uteri that we are encountering. The number is amazing.

PREGNANCY AND CARDIAC OPERATIONS*

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OBSTETRICAL rehabilitation, by cardiovascular surgery, has reopened the question of risk for the pregnant patient with congenital or acquired cardiac disease. Insufficient time and experience limit knowledge essential to the management of these groups. From observations made upon limited groups of patients who have had commissurotomy for mitral stenosis¹⁻²⁴ optimistic views have been expressed. Obstetrical experience with patients who have congenital cardiac disease has been only scantily documented.^{1, 25-34}

Hardly any physiological measure can test cardiac capacity as can pregnancy. In this era of increasingly successful cardiac operations, there come for re-evaluation such questions as the necessity for sterilization and/or therapeutic abortion, the operative risk versus the risk of conservative management for the pregnant patient with heart disease, and the risk to the fetus.

Material

The experiences herein recorded report data on 22 white patients who were subjected to various cardiac or cardiovascular operative procedures prior to or during pregnancy. Three categories are represented: mitral stenosis of rheumatic origin, 16 cases; tetralogy of Fallot, 3 cases; and patent ductus arteriosus, 3 cases.

All told, 51 pregnancies occurred: 26 prior to the surgical procedure and 25 afterward. Six patients were operated upon while pregnant. Before operation, 17 pregnancies accounted for 15 single term infants, one set of twins, and one deadborn infant. Seven pregnancies terminated in spontaneous abortion, and 2 were interrupted by therapeutic abortion. Following operation, 10 term and 4 premature infants were delivered. Two premature infants failed to survive. Spontaneous abortion occurred 5 times, and intragestational hysterectomy for therapeutic abortion and sterilization was performed twice. Four patients are undelivered.

Indications for Operation.—The indications for operation varied for the three groups. In the patent ductus arteriosus group, 2 nonpregnant patients suffered from mild (Class II) reduction in cardiac tolerance. Recovery from subacute bacterial endarteritis was a determining factor in one patient. The third patient, 5 months pregnant when subjected to division of patent ductus arteriosus, demonstrated no loss in functional cardiac reserve.

The tetralogy of Fallot group was characterized by cyanosis from birth and severe (Class III) limitation of physical activity.

*Presented at the Twenty-third Annual Meeting of the Central Association of Obstetricians and Gynecologists, Columbus, Ohio, Oct. 6, 7, and 8, 1955.

In the rheumatic mitral stenosis group, actual or threatening severe deterioration of cardiac reserve constituted the precipitating indication for commissurotomy. A major break in cardiac compensation during the present, or in a previous, pregnancy forced the issue in favor of operation for 7 patients. Cardiac decompensation unrelated to pregnancy served as an indication for 9 patients.

Age.—The group variation for the age when operation occurred was as follows: tetralogy of Fallot, 19, 21, and 14; patent ductus arteriosus, 27, 17, and 16; and for mitral stenosis, the average age was 30 years.

The average age when pregnancy occurred following the Blalock procedure was 22, following ligation of patent ductus arteriosus, 24, and following commissurotomy, 32 years. When commissurotomy was performed during pregnancy, the age averaged 29 years.

Operation in Relation to the Time of Gestation.—Five patients were subjected to commissurotomy during pregnancy: one each at 2, 12, 16, 20, and 23 weeks' gestation. Division of patent ductus arteriosus was accomplished when one patient was 20 weeks pregnant. In no instance was the pregnancy disturbed.

Time Interval Between Operation and Pregnancy.—For those patients who became pregnant following the cardiac or cardiovascular procedure, the time interval varied from one to four years following commissurotomy, for as long as ten years following division of patent ductus arteriosus, and from two to four years after performance of the Blalock procedure.

The suggestion³⁵ that commissurotomy may contribute to reactivation of rheumatic carditis and its sequelae was not borne out in this small group.

Before commissurotomy, classification of cardiac reserve placed 5 patients in Class II, 10 in Class III, and 1 in Class IV. The operative procedure upgraded all except 2 Class III patients in whom the operative result was unsuccessful. Their pregnancies were therapeutically interrupted by hysterectomy. In one other patient the surgical result was of limited success, and her cardiac reserve deteriorated from Class II to Class III during pregnancy.

Of the 13 patients in whom the operative result was considered successful, all except one remained in Class I during pregnancy and delivery. The one patient who showed deterioration in cardiac reserve from Class I to Class III became pregnant 2 years following successful commissurotomy.

Report of Cases

Patent Ductus Arteriosus.—

CASE 1.—A. T., was operated upon at the age of 27 years after having been under the care of a cardiologist for nine years because of Class II limitation of physical activity. Following division of patent ductus arteriosus, her functional status naturally changed to Class I. She was married one year after the operation and became pregnant for the first time four years later. She was delivered of her first child, a 3,450 gram infant, at term by means of midforceps under pudendal block anesthesia after four hours of normal labor. Her functional cardiac classification during pregnancy and delivery remained Class I. Her prenatal course was normal.

CASE 2.—B. L. was operated upon for division of patent ductus arteriosus at the age of 17 following treatment for subacute bacterial endarteritis. The functional result of the surgical procedure was excellent. At 23, however, she again proved to have positive blood cultures, again was cured following the administration of antibiotic therapy. She married at the age of 25 and became pregnant two years later. Her prenatal course was

entirely uneventful with unrestricted physical activities, and she was delivered at term under pudendal block anesthesia with the aid of midforceps after full dilatation of the cervix of a normal, living 3,460 gram infant.

CASE 3.—D. S., at age 16, at the time of division of patent ductus arteriosus, was discovered to be five months pregnant. The functional classification prior to and after operation was Class I. Her tolerance to the first two trimesters of pregnancy has been uneventful. She has not been delivered at the present time.

Tetralogy of Fallot.—

CASE 4.—M. M. suffered from severe cyanosis from birth. A Blalock procedure in another hospital was attempted, but a functioning shunt was not produced. Her functional classification prior to and after operation was III. She married at age 20, and she became pregnant at 25. Activities were limited to those of Class III for the first two trimesters and Class IV for the last trimester.

At 37 weeks' gestation the membranes ruptured spontaneously, and she was delivered under pudendal block anesthesia with the aid of low forceps after a labor of 157 minutes. The living premature infant, weighing 2 pounds, 9 ounces, survived.

The following year she again became pregnant. Again her cardiac status deteriorated and she was a bed patient for almost the duration of the pregnancy. The infant died in utero at the thirtieth week of gestation. While receiving oxygen she spontaneously delivered a macerated deadborn infant weighing 940 grams at 33 weeks without the aid of analgesia or anesthesia. Her immediate postpartum condition was extremely precarious, made more so by excessive digitalis. She has remained in Class IV since delivery. Her course emphasizes the hazards of pregnancy in unrelieved tetralogy of Fallot.

CASE 5.—P. W., a "blue baby" at birth, was married and became pregnant at the age of 18. Her functional cardiac status was Class III. The pregnancy was interrupted, and the Fallopian tubes ligated. At the age of 21 she was operated upon by the Blalock technique, and her cardiac function was upgraded to Class I. At the age of 23 years, she underwent tuboplasty to overcome infertility. Shortly after this operation she became pregnant but aborted spontaneously at two months. No subsequent pregnancy has occurred.

CASE 6.—V. R., a "blue baby" at birth, Class III functional activity, was subjected to the Blalock procedure at 14. Her cardiac functional status improved, and she required only the slightest limitation of activity. At 19 she was married and soon became pregnant. Her cardiac tolerance remained Class I throughout pregnancy and delivery. She was delivered at term of a 7 pound, 14 ounce infant with the aid of low forceps and pudendal block anesthesia after twelve hours of moderately severe labor.

Mitral Commissurotomy During Pregnancy.—

CASE 7.—E. J. developed a single attack of rheumatic fever at 11. At 17 she began medical care for rheumatic heart disease and was placed in Class I. At 23 she married and became pregnant two years later. In the second trimester her cardiac tolerance deteriorated, and she was placed in Class III the last four months. Her cardiac tolerance at delivery was under extreme stress. She was delivered while in an oxygen tent. Low forceps and pudendal block anesthesia were employed in the delivery of a 7 pound, 12 ounce living infant after 6 hours, 23 minutes of "easy labor." She developed acute pulmonary edema within the first six hours and was in critical condition under full digitalization and continuous 50 per cent oxygen atmosphere by tent for the next four days. Improvement to Class II was gradual.

She became pregnant the following year. When four months pregnant she submitted to commissurotomy for mitral stenosis with sufficient improvement in functional cardiac tolerance to be placed in Class I. At six and one-half months the membranes ruptured

spontaneously and a living, premature infant was delivered after 137 minutes of easy labor without the aid of anesthesia or analgesia. The infant did not survive. Cardiac tolerance was considered unlimited during the labor and postpartum periods.

CASE 8.—E. C. was discovered to have severe mitral stenosis of rheumatic origin at the age of 27 when she developed acute pulmonary edema. At 34, after being married two years, during which time she was severely limited in physical activity, she became pregnant. Her cardiac tolerance to pregnancy was very poor, and the infant was delivered spontaneously at four months after premature rupture of the membranes. Following delivery, her cardiac tolerance failed to improve, and she remained in Class III when she again became pregnant. She submitted to commissurotomy at 35 when two months pregnant, with immediate improvement in her functional capacity to Class I. Soon after her heart operation, she obtained office employment and worked full time without limitation until 7½ months pregnant. She was elated with her improvement and wrote an article, "My New Life," for publication in a popular women's magazine. Without cardiac distress, she delivered at term a live infant weighing 2,670 grams. Delivery was accomplished with the aid of low forceps and pudendal block anesthesia after two hours of moderately severe labor.

CASE 9.—G. D. developed acute cardiac insufficiency at the age of 42 during her fourth pregnancy at 7½ months. The history disclosed one term pregnancy 12 years previously and two subsequent pregnancies terminated by spontaneous abortion at three and four months. Her cardiac functional capacity was III for the remainder of her fourth pregnancy. While in critical condition she was delivered at term with the aid of low forceps. Her functional cardiac activity improved somewhat following delivery. She again became pregnant the following year at 43. She experienced severe limitation of physical activity and was in Class III. At five months' gestation she was subjected to mitral commissurotomy with dramatic improvement in functional capacity. During the remainder of her pregnancy she was considered in Class I and delivered at term an infant weighing 7 pounds, 8 ounces, with the aid of low forceps and nitrous oxide-oxygen anesthesia. There was no evidence of cardiac insufficiency after two hours of moderate labor. Her postpartum course was uncomplicated. Six months following delivery she experienced cardiac insufficiency and was again placed in Class III.

CASE 10.—C. B. first became aware of cardiac difficulty at 21 following an attack of dyspnea. She was married shortly following this episode and soon became pregnant. This pregnancy terminated in spontaneous abortion at 2½ months. The following year she again became pregnant, and symptoms of cardiac insufficiency became distressing. She was placed in Class II. Mitral commissurotomy was performed during the third month of pregnancy without difficulty. Her tolerance to physical activity improved, and she remained in Class I through the second trimester. She is undelivered.

CASE 11.—V. K. developed rheumatic fever at 9, but suffered no evidence of cardiac difficulty until she was 18, when she noticed increasing breathlessness on exertion. Hemoptysis occurred, and she found it necessary to use two pillows at night. She was married at 19 and soon became pregnant. During the twenty-first week of gestation at 2:00 A.M. on July 7, 1955, she developed paroxysmal dyspnea and serious pulmonary edema. Heroic treatment, including phlebotomy of 600 c.c., improved the immediate critical condition. Mitral valvulotomy was performed during the twenty-third week of gestation with immediate dramatic improvement in cardiac functional capacity. She is undelivered.

Pregnancy Following Commissurotomy.—

CASE 12.—R. V. developed multiple bouts of rheumatic fever at the age of 17. She was married at 24 and delivered three term infants without complicating cardiac difficulty in the ensuing six years. At 30 she developed cardiac insufficiency and was considered to be in Class III. At age 30 she was subjected to commissurotomy with good results. When

31, she became pregnant and aborted spontaneously at two months. When 34 years old, she became pregnant and spontaneously delivered a term infant without evidence of cardiac difficulty.

CASE 13.—H. T. was discovered to have mitral stenosis at the age of 20. She developed great difficulty in breathing and intermittent episodes of pulmonary edema. After being married for one year, during which time no pregnancy occurred, she was subjected to commissurotomy at 22. The successful surgical result converted her from Class III to Class I, and she became pregnant two years later. Her pregnancy progressed uneventfully until the sixth month of gestation when her functional cardiac status deteriorated from Class I to Class III. She was delivered at term, spontaneously, under the influence of caudal anesthesia while receiving nasal oxygen. Her postpartum response was satisfactory.

CASE 14.—E. T. was known to have contracted rheumatic fever at 13. She experienced cardiac insufficiency at 17. Her condition was well controlled under medical management and she was married at 32.

The following year she experienced severe, acute cardiac insufficiency and was placed in Class II after digitalization. At 34, she underwent commissurotomy with excellent results and was placed in Class I. Prior to operation she had one pregnancy which terminated in delivery of a deadborn infant at term after a "long labor." At 36, two years after commissurotomy, she became pregnant. Her tolerance to this pregnancy was excellent, and she remained in Class I during her entire pregnancy and delivery.

CASE 15.—C. B. developed a single attack of rheumatic fever at 13. At 17, it was necessary for her to have medical care for cardiac symptoms. When she was 18, during the fourth month of pregnancy, she had her first attack of cardiac decompensation. This pregnancy terminated in spontaneous delivery of a term infant after a short labor. Her activities were drastically limited during this pregnancy, and she was considered as in Class III. Following delivery, her functional status improved, and at 20 she was subjected to commissurotomy for mitral stenosis. Her functional status improved to Class I following operation. At 22 she became pregnant. Her tolerance to pregnancy was excellent, and she continued in Class I for all three trimesters. She delivered prematurely at 7 months' gestation. Her labor lasted 99 minutes and terminated spontaneously, without analgesia or anesthesia. The infant survived.

CASE 16.—J. L. was delivered of her first child at 20. When 33, she became pregnant and aborted spontaneously a pregnancy of 3 months' gestation. When 36, she suffered her first attack of mitral insufficiency characterized by shortness of breath, nocturnal dyspnea, and pulmonary edema. Following this, her physical tolerance was limited to Class III. When 38, she underwent mitral commissurotomy with good results. Marked improvement in functional activity followed, and she was placed in Class I. The following year she became pregnant and aborted spontaneously at 3½ months' gestation. Her physical tolerance remained Class I during the gestation period.

CASE 17.—A. V. suffered repeated attacks of rheumatic fever as a child. She first developed acute cardiac decompensation at 22 years during the first pregnancy. Her functional tolerance through this pregnancy was considered Class III, and she delivered vaginally at term in very critical condition. During the next four years she improved under constant cardiological supervision and experienced no distress from ordinary physical activity. When she was 26, she again became pregnant with therapeutic interruption at two months' gestation. Her cardiac status was considered as being Class II at that time.

Mitral commissurotomy for pure mitral stenosis was performed successfully several months following therapeutic abortion with improvement in her functional status of sufficient degree to permit her being classified in Class I. A spontaneous abortion of 3 months' gestation occurred shortly following cardiac operation. The following year at the age of 27 years, she

deliberately undertook a fourth pregnancy and is undelivered at the present time. Her tolerance to the present pregnancy has been excellent. No restriction of physical activity has been necessary during the observed first two trimesters.

CASE 18.—E. F. gave no history of rheumatic fever, but pure mitral stenosis was discovered in her early 20's. Her first pregnancy occurred when she was 21 and terminated in vaginal delivery of a term infant with no cardiac symptomatology. At the age of 23 and again at 25, she experienced spontaneous abortions at about 3 months' gestation. Evidence of increasing cardiac insufficiency gradually developed over the next few years which required Class II restriction of physical activity. When 33, she submitted to mitral commissurotomy with incomplete recovery of functional cardiac capacity. Prior to pregnancy at age 36 her functional status was considered Class II. Atrial fibrillation developed during pregnancy, and its control became increasingly difficult as pregnancy progressed. During the second and third trimesters of pregnancy, decreased function was evident and she was placed in Class III. Hemoptysis occurred once during the second trimester. Delivery occurred at term with the aid of low forceps and pudendal block anesthesia after 11½ hours of labor. The infant weighed 8 pounds, 4 ounces.

CASE 19.—M. K. developed rheumatic fever at 4 years of age. When she was 24 she suffered an initial attack of acute cardiac decompensation characterized by hemoptysis, pulmonary edema, and severe breathlessness. Mitral commissurotomy was performed when she was 30. Three years later she became pregnant for the first time and tolerated the pregnancy and delivery as in Class I.

CASE 20.—G. D. developed rheumatic carditis with insufficiency at 15. Recovery was incomplete, and she was considered to be in Class II. At 27 she submitted to commissurotomy.

Prior to cardiac surgery she had two pregnancies at 21 and 23. During both pregnancies, she experienced added cardiac difficulty but delivered spontaneously at term each time. One year after commissurotomy she became pregnant for the third time. Her functional cardiac classification at the onset and during pregnancy has remained Class I. She is undelivered.

Cardiac Surgery and Therapeutic Abortion.—

CASE 21.—M. P. had a single attack of rheumatic fever at 16. She was married at 23, and at 25 became pregnant for the first time and delivered twins at term. During this and her subsequent pregnancy four years later, she experienced critical cardiac insufficiency, and both times was considered as in Class III. At 34 years she developed acute cardiac insufficiency characterized by hemoptysis, pulmonary edema, and breathlessness. When 38, she submitted to mitral commissurotomy for stenosis and insufficiency. At operation, the mitral valve was discovered to be fibrotic, hard, and firmly contracted, precluding adequate commissurotomy.

Pregnancy occurred the following year at age 39. The additional hemodynamic load of pregnancy was soon evident clinically, and the case was submitted to the Therapeutic Abortion and Sterilization Board with the cardiologist's recommendation for therapeutic abortion and sterilization. The Board agreed, and the pregnancy was terminated by complete hysterectomy when the patient was four months pregnant. She tolerated this operation without difficulty.

CASE 22.—M. H. developed rheumatic fever at 11 years of age. Until she was 37, she experienced little evidence of impaired cardiac function. Then, following within two hours of spontaneous delivery of a 2,770 gram infant, after a mild labor of 96 minutes, she developed acute pulmonary edema. Prompt emergency therapy resulted in survival of an emotionally traumatized patient. Her recovery was incomplete, and she was placed in Class III.

The following year at 38, she submitted to mitral commissurotomy for stenosis and insufficiency. The mitral valve was thickened, hard, and unsatisfactory for surgical success. Following the operation, her functional status improved slightly, and physical

activities could be liberalized to regroup her into Class II. She became pregnant the following year. Therapeutic abortion and sterilization were advised by the cardiologist in which opinion the Therapeutic Abortion and Sterilization Board concurred.

The five months' pregnancy was interrupted by complete hysterectomy performed under general anesthesia. This procedure was tolerated without additional distress.

Comment

Indications for Cardiac Surgery During Pregnancy.—Both Mendelson²² and Glover and associates²¹ consider mitral stenosis patients in Classes III and IV candidates for mitral commissurotomy during pregnancy. To these should be added that group of patients who previously experienced an acute episode of cardiac decompensation either during pregnancy or immediately following delivery. These patients frequently improve once the hemodynamic burden of pregnancy is removed, and regrading upward to Class II or even I may be possible. Operations upon the heart and the great vessels are frequently avoided until the onset of another pregnancy.

The indications for operation during pregnancy for patients suffering from patent ductus arteriosus and other types of cardiovascular disease including tetralogy of Fallot are less precisely defined. The one patient operated upon for division of patent ductus arteriosus demonstrated the possibility of this operation being performed during gestation. Although not included in this report, surgical correction of coarctation of the aorta has been done during pregnancy.^{25, 26, 27, 29, 30} Eastman,²⁸ in an editorial comment, cited a patient who died several months following surgical repair of coarctation of aorta as the result of rupture at the site of anastomosis. Eastman feels that the risks from operation are greater than the risks from good obstetrical management, and he states that he would be inclined to postpone surgical correction of coarctation of the aorta until six months after delivery.

Time of Optimum Safety.—If cardiac operation is to be performed during pregnancy, the time of optimum safety is important. Two danger periods are faced by the pregnant patient with heart disease.¹⁰ The first is experienced during the time interval immediately prior to 32 weeks' gestation when the acclivity gradient of increasing cardiac load is steepest. Adams,³⁶ using a dye dilution method of evaluating cardiac output during gestation, showed results which are in agreement with those of others^{14, 17, 18, 38} in demonstrating that the acme of cardiac work is at that time. Thereafter, the work load gradually decreases. Yet the total blood volume to be mobilized by cardiac action remains essentially stable.

Studies by Hodgkinson^{39, 40} showed alterations in the uteroovarian veins as the result of pregnancy to consist of physiological hypertrophy and dilation of the lumen of the veins. Such changes dissipate the tendency to increased pressure resulting from augmented blood volume. In physiological effect, these changes in the walls of the veins serve to shuttle a considerable segment of the blood volume out of the active systemic circulation, thereby serving somewhat as a damping mechanism for the tendency to raise venous pressure. Sampson⁴¹ designated the uteroovarian veins an example of a "human sponge" to emphasize their ability to fill with blood during pregnancy.

The next major challenge to cardiac function occurs with myometrial contraction following delivery. This uterine action suddenly empties the contents of the uteroovarian veins into the systemic circulation. Mobilization of this abruptly augmented blood volume may be a function beyond the capability of a damaged heart. Severe pulmonary edema may develop.

The decision to operate depends upon the urgency for upgrading cardiac function. Admittedly, the risk is less in the early weeks of pregnancy before

work load of the heart is increased to a dangerously high level. Yet, when the cardiac status of the patient is most precarious, near the thirty-second week, the results achieved may be most brilliant.

Clinical experience shows that the heart of the gravid patient may be safely operated upon by commissurotomy at any week of pregnancy. O'Connell and Mulcahy²³ reported an operation upon a patient at term twelve hours before delivery. Neither the feared precipitation of abortion during the early months of gestation nor the anesthetic-induced intrauterine death of the fetus have been observed.

The final decision to operate upon a pregnant patient with heart disease rests upon the combined opinions of the cardiologist, the cardiac surgeon, and the obstetrician. This deliberation must consider every facet of risk should the patient continue in her pregnancy without operation on the diseased heart, balanced against the risk of possible operative mortality. As a result, most pregnant patients upon whom commissurotomy is performed have rather urgent indications. Patients with less seriously impaired hearts are usually carried on conservative management with safety.³⁷

Cardiac Capacity Following Operation.—The potential gestational cardiac reserve of the patient operated upon prior to pregnancy is less well documented than for the patient operated upon during pregnancy. As might be expected, patients who become pregnant following division of patent ductus arteriosus demonstrate little or no alteration from the normal.

The prognosis for cardiac reserve during pregnancy following operations for tetralogy of Fallot must be guarded until additional reports are available. It is encouraging to report a pregnancy and delivery tolerated by one patient without serious difficulty. Another patient, whose operative result was unsatisfactory, tolerated two pregnancies poorly. The third patient aborted spontaneously when 14 weeks pregnant and displayed no deterioration of cardiac reserve during the time she was under observation.

It is not possible from this limited experience to predict the tolerance to pregnancy following operations for tetralogy of Fallot. Some indication of the expected behavior during pregnancy may be surmised from the technical success and clinical improvement resulting from operation. The ability to withstand average physical activity lends optimism to the indication of what might expected should the patient become pregnant.

The obstetrical capabilities of patients subjected to commissurotomy are unpredictable. The late results²¹ of mitral commissurotomy may be influenced by adverse technical factors related to the selection of patients for commissurotomy: age over 40, atrial fibrillation, associated aortic valve disease, associated valvular insufficiency, preoperative valve size of more than 1 sq. cm., postoperative valve size of less than 2.5 sq. cm., and calcification of the valve. In listing these seven adverse factors, Harken,³⁵ emphasized the need for prolonged rigid medical regimen following operation. He further stated that postoperative mitral insufficiency, restenosis, embolic phenomena, reactivation of rheumatic fever, and a poor surgical result are sequelae suggesting a guarded cardiac prognosis. Regressive cardiac function in the interval between operation and pregnancy could lead to uncertainty in predicting cardiac reserve.

The postcommissurotomy syndrome, considered by some to be evidence of reactivation of rheumatic fever, and by others³⁵ to be a manifestation of surgical trauma, was not seen in this group of patients. Neither were restenosis, mitral insufficiency, embolic phenomena, nor reactivation of rheumatic fever

observed. The observation of Glover and associates,²¹ that the state of pregnancy may protect a patient against rheumatic activity was not revoked by observation of this group of patients.

The most important determining factor for successful tolerance to the circulatory stress of gestation in these sixteen patients suffering from mitral stenosis was a technically successful operation. With any result short of technical success, the tolerance to pregnancy was limited, and cardiac efficiency progressively deteriorated as the hemodynamic burden increased.

Management.—The obstetrical management of patients previously subjected to cardiac surgery should be the combined effort of the cardiologist, cardiac surgeon, and obstetrician. Improved cardiac tolerance following operation should in no way detract from interest by any of the three services. The patient should continue to be considered in the category of the pregnant patient with heart disease and receive all the care and consideration usually given to this important group of patients.

Prophylactic antibiotic therapy is considered advantageous during labor and delivery. In our experience, vaginal delivery with minimal predelivery sedation, second stage forceps application, early episiotomy, and pudendal block anesthesia have been considered wise.

Particular attention must be given to the immediate twelve-hour postpartum period. Tachycardia, orthopnea, and basal râles may forewarn of acute pulmonary edema of sudden left heart failure. Large-volume infusions should be avoided and sodium intake restricted.

The role of therapeutic abortion and sterilization for the cardiac patient has been simplified by the advent of successful cardiac surgery. Successful surgical results prior to or during pregnancy in any type of heart disease suitable for surgical treatment make the recommendation of these measures unnecessary provided the patient can be restored to good functional activity. By the same measure, unsuccessful cardiac surgery in a patient severely limited in her physical activity prior and subsequent to operation is substantial evidence that she will withstand the augmented hemodynamic burden of pregnancy poorly, and she should be considered as a candidate for therapeutic abortion and sterilization. No therapeutic abortion and sterilization board should consider the question of their intended function in any female patient with heart disease in the childbearing age, whether she is pregnant or not pregnant, without first obtaining the opinions of a competent cardiologist and cardiac surgeon.

Summary and Conclusion

Twenty-two patients subjected to cardiac operations prior to or during pregnancy are discussed from an obstetrical standpoint. Division of patent ductus arteriosus was performed in one patient when she was 20 weeks pregnant, and in 2 patients prior to pregnancy. All were converted to Class I. The patient operated upon during pregnancy is undelivered, while the other two patients uneventfully delivered term infants.

The Blalock procedure for tetralogy of Fallot was performed 3 times. The operative result was not successful in one case. This patient's subsequent 2 pregnancies were accompanied by critical deterioration in cardiac reserve. Both times the infants were delivered prematurely. The other 2 patients were improved to Class I. One patient aborted spontaneously when 14 weeks pregnant while the other delivered uneventfully a term infant following a normal pregnancy.

There were 16 patients who had rheumatic mitral stenosis. Commissurotomy was performed during pregnancy in 5 patients, and prior to pregnancy in 11 patients. Those operated upon during pregnancy were upgraded to Class I and remained so during the period of gestation and delivery. Two are undelivered. One delivered prematurely following spontaneous rupture of the membranes at 7 months' gestation, and 2 delivered normal term infants. Pregnancy followed commissurotomy in 9 patients. Two received no surgical benefit and were subjected to hysterectomy during the second trimester. Another improved partially from operation but demonstrated progressive cardiac deterioration during pregnancy. She delivered at term while under strict medical management. A fourth patient suffered deterioration in cardiac reserve, and concluded her pregnancy at term while on a strict medical regime. Of the 7 remaining, all Class I, 2 are undelivered, 2 aborted spontaneously at 3½ months, 1 delivered prematurely when 7 months pregnant, and 2 delivered term infants.

This experience has demonstrated that for all three groups the potential gestational cardiac reserve was most accurately indicated from the degree of improvement resulting from the operation; that a successful operative result usually indicated an excellent pregnancy potential, while a lesser result was associated with cardiac deterioration during pregnancy.

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Discussion

DR. HOWARD J. TATUM, New Orleans, La.—The data presented indicate that the deleterious effects of pregnancy upon the patient with congenital or acquired heart disease can be largely eliminated by means of definitive cardiac surgery. On the other hand these data do not offer great encouragement in so far as fetal salvage is concerned. There were 26 pregnancies prior to cardiac surgery. Of these, 16, or 62 per cent, resulted in living children. In 25 pregnancies following cardiac surgery 12, or 48 per cent, terminated in living children. If we include 5 patients who are as yet undelivered, a maximum fetal salvage of 68 per cent could be attained. This may be an unfair comparison inasmuch as several of the pregnancies prior to operation occurred before symptomatic and functional heart disease was present. If, then, we include for this comparison only those patients with cardiac signs and symptoms during their pregnancies prior to operation we find that there were 11 such pregnancies and 10 living babies for a 91 per cent (82 per cent if a twin pregnancy had been a single pregnancy) salvage. The theoretically maximum fetal salvage of 68 per cent in the 25 pregnancies following cardiac surgery is not very encouraging by comparison.

The incidence of spontaneous abortions, although relatively high before and after cardiac surgery, did show a moderate decrease following operation. I would like to ask Dr. Igna if he believes that the relatively high incidence of spontaneous abortions which occurred following operation is a sampling artifact or is there an unknown factor in the patient with heart disease, excluding decompensation, which predisposes to early spontaneous termination of pregnancy.

From the data presented in this extremely interesting paper one must conclude that much more evidence will be necessary before a potential mother with heart disease should be encouraged very strongly to accept cardiac surgery for the primary purpose of increasing her capabilities of producing a living child.

DR. OLGA HANSEN LITZENBERG, Minneapolis, Minn.—My comments are not of the constructive kind because I have nothing to add except those of a very enthusiastic viewer of the race—the race for saving the mothers and babies, and the human race in general.

Considering the short period of time that cardiac surgery has been done, a great deal has been contributed. I do not think that a year ago, when I went over these statistics (those published), I would have been able to find any one series of more than a very few cases. It was most encouraging and impressive to see a series of this sort well documented.

DR. IGNA (Closing).—We too have pondered Dr. Tatum's question, and we have not been able to come up with an answer.

If you will notice the age at which mitral commissurotomy is performed prior to pregnancy, you see the age group is 32. Most of these patients became pregnant anywhere from two to four years later, and I think the group is so small that we cannot definitely say whether age might enter into it.

The operation itself does not cure mitral heart disease. It improves the physiology because of removing the pulmonary hypertension. Whether that enters into it, I do not know.

RELAXIN, THE THIRD OVARIAN HORMONE: ITS EXPERIMENTAL USE IN WOMEN*

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ONE of the intriguing and perplexing problems of gynecic endocrinology today is the proper placement of relaxin, a nonsteroid hormone first identified in association with gestation, whose effects were originally considered as the product of the corpus luteum hormone. Although there may be discussion about the precedence in the discovery of the ovarian hormones,²¹ priority is usually awarded to Allen and Doisy⁴ for their isolation of the estrogenic hormone in 1923, and to Corner and Allen⁸ who described the progestational effects of the corpus luteum extracts in 1929. Almost simultaneously Hisaw and associates¹⁷ identified a corpus luteum extract which produced progestational effects in monkeys. Hisaw reported many effects from the corpus luteum extract, including growth and relaxation of the pelvic ligaments of the guinea pig. This was described as the distinct effect of a new ovarian hormone in 1929.¹⁶ Since then, work on this elusive substance has proceeded fitfully and irregularly.

Species specificity apparently modifies the effects of this hormone. Several factors (guinea pig, mouse, symphysis-relaxing, uterine-relaxing and others) have been referred to, but their exact status is not clear. All are included in relaxin. At the 1955 meeting of the Endocrine Society Kliman and Greep¹⁹ as well as Frieden and Noall¹² helped somewhat to clarify the issue when the former showed that the mouse-active ovarian fraction represents a more slowly mobilized form of relaxin. The latter authors reported that the varied fractions appear to be distinct by chromatography and by counter current distribution, but complete separation has not been achieved. Hisaw and Zarrow¹⁸ have capably described the background of relaxin research and assay, whereas Frieden and Hisaw¹¹ have reported the biochemistry of relaxin. This latter pair considered relaxin to be a polypeptide or simple protein, with a molecular weight of less than 10,000. Activity seems to depend on the disulfide groups of cysteic acid (cysteine or cystine), and on the presence of free carboxyl ($-\text{COOH}$) groups. This evidence is considered by some as debatable and uncertain, however. This is the problem which at present confronts the biochemists. Only that extract which is standardized by and

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identified as producing relaxation of the symphysis in the estrogen-primed castrate guinea pig* will be considered as relaxin for the balance of this discussion.

This drug, which satisfies the classical description of a hormone, was first identified in corpus luteum extracts. Currently, the ovary of the pregnant sow is the source of the most potent material, but extracts of corpus luteum and residual ovary are equally active.³ Pregnant rabbit serum may contain up to 10 guinea pig units (GPU) per cubic centimeter. In the rabbit, the maternal placenta, fetal placenta, ovaries, uterus, and vagina contain relaxin in that order of concentration.²⁴ The basic material has also been found in sera of pregnant women (1 to 2 GPU per cubic centimeter), while extracts of term human placentas have shown only trace activity.²³ In humans and test animals relaxin disappeared rapidly from the blood, and was undetectable within twelve hours of delivery. Experimentally it required 1,000 to 4,000 GPU at 3 to 8 hour intervals to produce a blood level of 1 to 2 GPU per cubic centimeter after 24 to 48 hours. Despite its apparent protein nature, antigenicity has not been a problem to date. Connective-tissue effects studied in guinea pigs⁶ and monkeys⁷ seem to indicate that relaxin produces a disaggregation or depolymerization of the ground substance, probably a glycoprotein.

The ability of injected relaxin to dilate the cervix has been reported for the cow¹⁴ and the pig.²⁵ Gassner¹³ has reported that marked cervical dilatation occurred in stilbestrol-primed cows with hydramnios during the 24 hour period in which they received 6,000 to 18,000 GPU relaxin. He also pointed out that oxytocin produces contractions without dilatation in the cow, and suggested that relaxin might trigger the dilating mechanism.

For some time the senior author has been interested in the possible production by hormones of the hydronephrosis and ureteral dilatation associated with the pregnant state. In the continuation of the human experiments, a supply of relaxin† was made available, and the remainder of this paper deals with our personal experiences with this product.

Experiments and Results

Ureteral Relaxation and Dilatation.—

Four groups of paired patients at Cleveland State Hospital were subjects. All were determined to have normal urinary systems by urinalyses, blood chemistry determinations, and pyelography.‡ The first pair was adolescent, the second sexually mature and parous, the third menopausal, while the last group was postmenopausal, one being a castrate. Special views of the symphysis were taken during the preliminary studies, and these views were repeated with each phase of the experiment at the time of subsequent pyelograms. Each subject was primed with five daily injections of 1 mg. estradiol.‡

*The intact animal is now used, and current techniques permit the use of the mouse as well. Symphysis growth may reach 6 mm. in twenty-four hours in this animal.²⁰

†Releasin, Warner-Chilcott brand of relaxin was kindly furnished by Dr. Robert Kroc. This material was first available at a strength of 1,000 GPU per cubic centimeter, which was gradually increased to 3,500 GPU per cubic centimeter. Releasin is now standardized in terms of milligrams of a relaxin standard, and 150 GPU is equivalent to 1 mg. of the standard. Depot relaxin (Repository Solution Releasin) was standardized in GPU, containing 2,000 GPU per cubic centimeter, but more recently is standardized in terms of the relaxin standard.

‡Neo-Iopax (Schering) and microcrystalline Progynon, Schering brand of estradiol U.S.P. were furnished through the courtesy of Dr. Norman Hemmingsway.

During the succeeding five days she continued to receive the daily injection of estradiol as she was given, in addition, 7,500 to 70,000 GPU relaxin daily in six divided doses so spaced that half the total dosage was given between 4 and 10 A.M. Pyelograms were taken on the third and fifth mornings of the combined treatment. Courses were repeated at 1 to 3 month intervals, depending on the response and rates of recovery of the patient.

After the fourth run, only the adolescent group was retained in the experiment, and these were used only in the progestational phase of the cycle. There had been no response in the two older groups, and the only suggestive responses occurred during the progestational phase in the youngest pair. At a daily dosage of 45,000 GPU a slight separation of the symphysis occurred (Fig. 1) in one subject (B. C., No. 9176) on the third day of treatment. An elongation of the right ureter was also present. Both effects were absent on x-rays taken on the fifth day of the same course of treatment, and neither effect could be duplicated with either increasing or decreasing doses of relaxin in later studies. This failure may have been an antihormone effect. Abramson, Caton, and Roby¹ reported pyelographic evidence of delay in filling of the ureter and bladder of estrogen-primed castrate hysterectomized rabbits by the

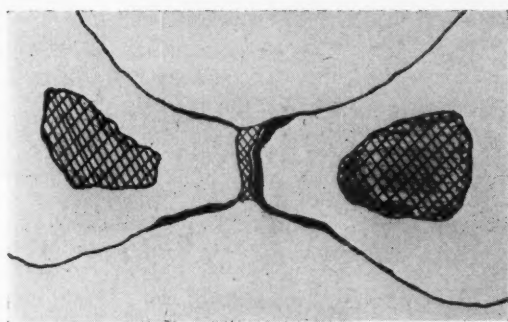


Fig. 1.—B. C. (C.S.H. No. 9176) Superimposed shadowgraphs of x-rays of symphysis before and after relaxin treatment. Cross-hatch is pretreatment separation, heavy black line is increased separation after treatment.

daily injection of 1,000 GPU for two weeks. Realizing the difference in techniques, we were unable to produce similar results in these patients, and the one next reported. Because of the apparent relationship of relaxin activity to pregnancy, a patient (D. McC., No. 56062) scheduled for therapeutic abortion at Mt. Sinai Hospital had a control pyelogram on the day of admission. On the following day she received approximately 120,000 GPU (800 mg. equivalent) in 120 c.c. sterile saline by intravenous drip during a 2 hour period preceding a second pyelogram. If there were any differences at all in the pre- and posttreatment films of the urinary tract, there was an apparent increase in the rate of filling of the lower ureters in the post-relaxin x-rays at 15 and 25 minutes. The later films are almost identical. There was no visible change in the symphysis.

Cervical Softening.—

During the study at Cleveland State Hospital, it was noted on several occasions that the experimental subjects developed a marked softening of the cervix. Since the induction of labor in a patient with an uneffaced and unripe cervix will often tax the ingenuity of the obstetrician, and since Calkins⁵ has shown that cervical softening expedites labor, the preliminary use of relaxin was tested in 32 patients at Mt. Sinai Hospital. These received approximately 7,500 GPU every 15 to 30 minutes for 6 doses, following which an

intravenous drip of dilute Pitocin (0.65 to 1.0 c.c. per liter of 5 per cent glucose in water) was started. Two additional injections of relaxin were given at half hour intervals after the start of the drip. Indications for induction varied from toxemia and diabetes to "convenience" of the patient and/or physician. Gestation varied from 31 weeks to "postmaturity." Stripping of the membranes, with or without artificial rupture, was done at the discretion of the obstetrician if labor did not supervene.

Successful induction followed by rapid labor occurred in the first 12 patients, whereas complete failure of the first attempt ensued in the next 8. Two had repeat courses with repeated failure. In almost all of these subjects, however, the cervix became so soft that it was almost impossible to determine dilatation or effacement with accuracy on rectal examination. On vaginal examination it was determined that extreme cervical softening did not necessarily lead to effacement. When labor did ensue, it was noted that progress to delivery was frequently very rapid, and often precipitous. Since this has been reported on occasion as the result of artificial rupture of the membranes as well as occurring with Pitocin inductions, we are not ascribing this to relaxin. It is our opinion, however, that relaxin did play an active part in the speedy progress of labor. In these patients relaxin did not appear to inhibit or detract from the effect of Pitocin. Neither did it with certainty enhance the ease or diminish the difficulties of induction in the patient with unripe cervix. Of the 32 subjects, labor was induced on the first trial in 22, on the second in 6, and on the third in one. Induction failed completely in 3, one of whom received two courses of relaxin-Pitocin. These results are approximately the same as those obtained by routine induction techniques at Mt. Sinai Hospital.

To verify the extreme cervical softening clinically apparent following the use of relaxin, this drug was given preoperatively to 2 patients requiring therapeutic abortion at 16 and 18 weeks' gestation. Each received 8,500 GPU every 6 hours for the first 3 doses, and every 2 hours for the next 2. The sixth and last dose was given "on call" to the operating room. Successful vaginal evacuation of these uteri was easily accomplished as the cervix was dilated to over 4 cm. without difficulty. Bleeding was within the normal range, and convalescence was uncomplicated in each case. There was no evidence of cervical damage at the first postoperative checkup examination. Both operators expressed the opinion that relaxin abetted the ease of cervical dilatation and permitted vaginal evacuation of a uterus which under other circumstances would have been emptied by hysterotomy.

As a further test, relaxin was given to 3 patients with "cervical dystocia" and to a fourth with a stenotic cervix and secondary inertia. Each received 7,500 to 10,000 GPU relaxin every half hour for 4 doses in place of morphine or Demerol. Intravenous glucose feeding was started at the same time. During the second hour of treatment labor stopped in each subject, and the uterus remained quiet up to two and one-half hours. When labor started again, 2 patients proceeded to rapid delivery, whereas pituitary extract was required to complete labor in the third. The fourth subject (D. G., No. 25536) had a known cervical stenosis secondary to Bovie conization of the cervix. Following relaxin-induced rest, labor was rapid and delivery simple. Postpartum examination of the cervix disclosed a disrupted portion (Fig. 2) lying free in the vaginal canal. The cervix appeared intact at the examination at six weeks post partum, as the point of rupture could not be found. Five other patients with primary inertia had normal progressive labor following relaxin injections, but without the appearance of the "relaxin rest." In each there was a definite modification in the type of painful contractions present. Unfor-

Unfortunately, technical and mechanical difficulties have interfered with our attempts at recording these changes by Lorand tokodynamometer. Painful contractions of prolonged false labor which eventuated in primary inertia and exhaustion of the patient were eased but not completely relieved in one subject (M. G., No. M-1366).

Delaying Progress in Labor.—

Since many of the patients who received relaxin in labor seemed to get a brief rest period which was often followed by rapid delivery, an attempt was made to determine whether or not this inhibiting effect, previously reported for the rat²² and guinea pig,¹⁰ could be extended in the human female to prevent the progress of undesired labor. This was defined as premature labor between the twenty-fifth and thirty-fifth weeks of gestation; and labor was defined as that associated with painful contractions, effacement, show, and increasing cervical dilatation. Bloody show was frequently present at the start of treatment, but descent of the presenting part was not always associ-

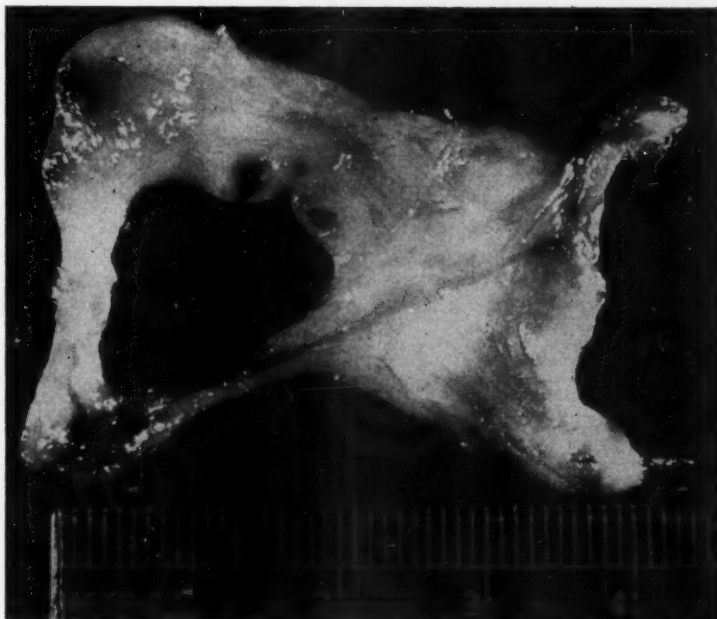


Fig. 2.—D. G. (M.S. No. 25536) Disrupted cervix found in vaginal canal after delivery. External os is intact. Photograph remade from Kodachrome.

ated with early labor. Spontaneous premature rupture of the membranes had occurred in 5 patients, and several others had irritable uteri accompanying vaginal bleeding. In all patients, infants in utero were alive at the start of treatment. This series is comprised of 13 patients (St. Ann Hospital—5, Mt. Sinai Hospital—8). The first 2 (St. Ann) were treated by injections of relaxin at 15 to 20 minute intervals to a total dose of 60,000 to 70,000 GPU over a 2 hour period. Labor slowed as contractions became irregular and weak for 90 minutes to three hours. This was followed by a rapid and uneventful delivery. The next 2 received relaxin diluted in 5 per cent glucose in water by intravenous drip at a rate of 40 to 100 drops per minute. The solutions averaged 7,000 GPU per liter. Active labor was never completely inhibited, but failed to progress until therapy was discontinued. Both patients were in active labor with 3 to 4 cm. cervical dilatation and bloody show at the start

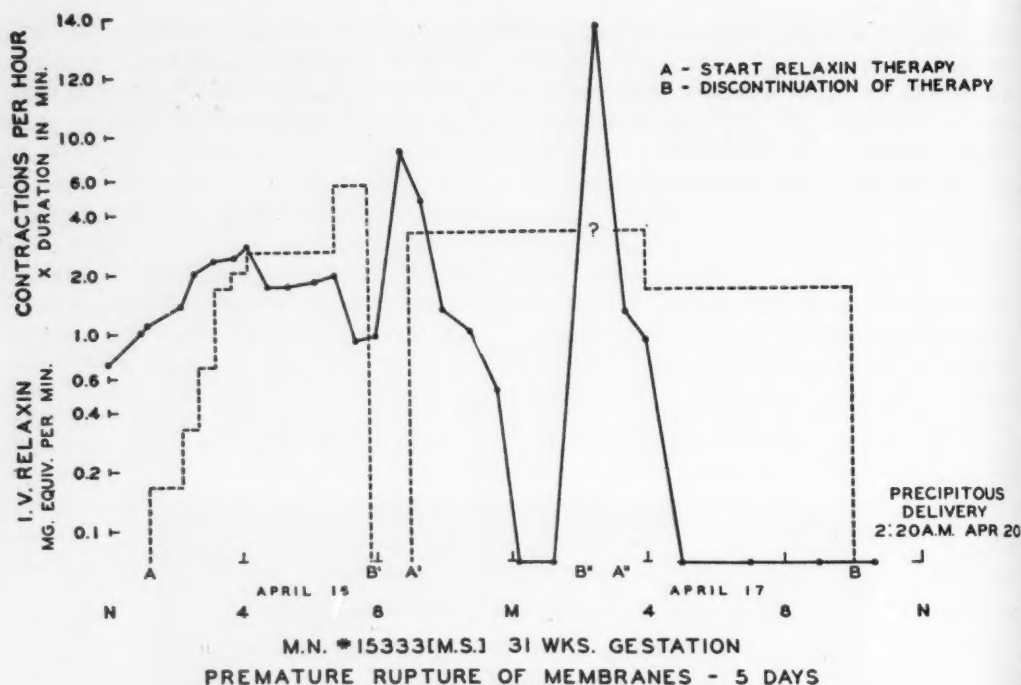


Fig. 3.—M. N. (M.S. No. 15333).

Figs. 3 and 4.—Semilogarithmic graphs demonstrating effect of relaxin on early labor.
----- Dosage of intravenous injection of relaxin.

————— Strength of labor (number of contractions per hour multiplied by duration of contractions in minutes).

A Original start of relaxin therapy

A' First restart of relaxin therapy

A'' Second restart of relaxin therapy

B Final discontinuation of relaxin therapy

B' First discontinuation of relaxin therapy

B'' Second discontinuation of relaxin therapy caused by infiltration

C Stilbestrol given 25 mg. every 15 minutes for 8 doses

D Demerol, 100 mg.

D' Demerol, 100 mg.

E Secobarbital, 200 mg.

of treatment. Membranes had been ruptured for one week in the first, at 31 weeks' gestation. Delivery in each patient occurred within 4 hours of the end of treatment. The last of the St. Ann Hospital subjects is of interest as she received three separate courses of relaxin, the first at 25 weeks' gestation. She had had two previous laparotomies for the conservative treatment of extensive endometriosis, and it was believed that scars and adhesions were the focal points for ectopic painful contractions. She was again treated at 29 weeks with resultant cessation of labor. She was delivered of a living male infant at 36 weeks by Dührssen incision and midforceps extraction after 36 hours of labor (D. P., No. N-1581). During this final labor, she had a 6 hour rest period induced by intravenous relaxin. This is the only patient who received more than two courses of intravenous relaxin at periods over 4 weeks apart. There was no evidence of sensitivity or toxicity.

Labor persisted in 3 of the 8 patients treated with intravenous relaxin at Mt. Sinai, and progressed to completion within 6 hours of admission, and within 2 to 4 hours of the onset of therapy. Three additional patients delivered within the first hour of treatment. Figs. 3 and 4 graphically describe the courses of labor in the last 2. Progressive labor was stopped by prolonged, high dosage.

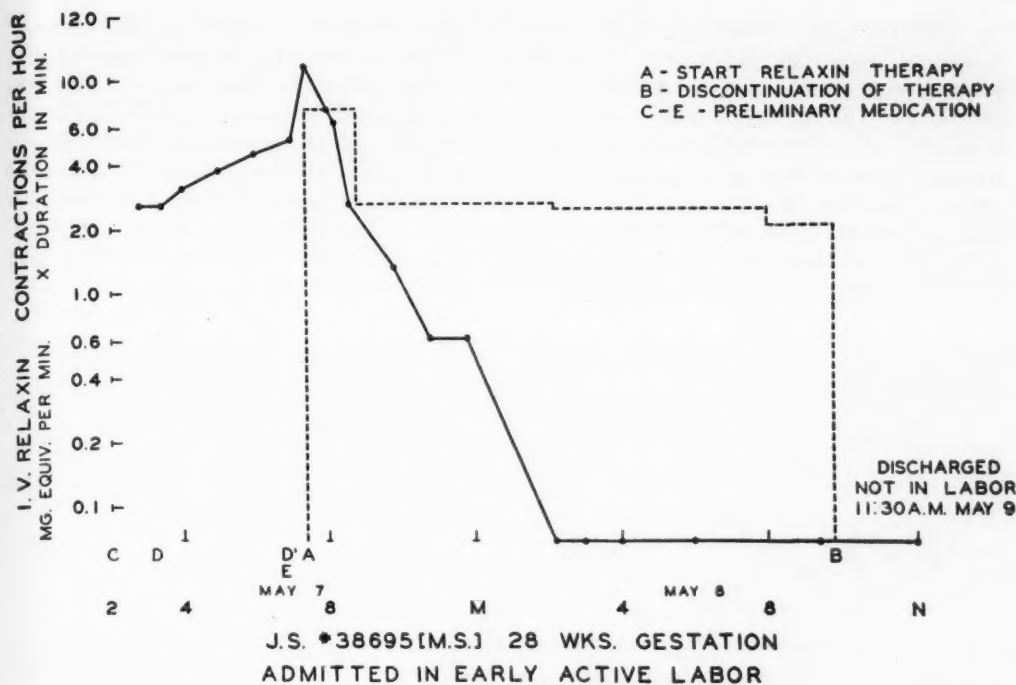


Fig. 4.—J. S. (M.S. No. 38695).

M. N., No. 15333, had lost her preceding pregnancy under similar circumstances of premature spontaneous rupture of the membranes at 30 to 31 weeks. High progesterone therapy had failed.⁹ When she was admitted at 31 weeks with ruptured membranes, treatment consisted only of bed rest with commode privileges at the bedside. Spontaneous labor started 5 days later. Despite increasing relaxin dosage labor progressed to regular 8 minute contractions lasting 30 seconds at a dosage rate of approximately 2.5 mg. equivalent of relaxin per minute. Contractions remained steady at this rate. When the fluid was discontinued, contractions increased to 4 to 5 minutes, lasting 45 seconds, and dilatation of the cervix was noted at 3 cm. Bloody show was present. Relaxin was restarted at slightly over 3 mg. per minute, and contractions slowed, stopping within 3 hours. Shortly thereafter, active labor recurred with a 3 to 4 minute interval and contractions lasted 40 to 45 seconds. The infiltrating relaxin drip was withdrawn and restarted. Labor slowed immediately, and this was maintained on a dosage of just under 2 mg. per minute of relaxin. Therapy was discontinued approximately 6 hours after the cessation of labor. Depot relaxin was continued for 24 hours by deep intramuscular injection. The patient awakened during the early morning of April 20, 36 hours after all treatment was discontinued, in active labor, and was delivered within the hour. The male infant lived.

The last patient, J. S., No. 38695, was admitted in early active labor with slight vaginal bleeding at 28 weeks. Administration of stilbestrol by the "Karnaky routine" was begun, and Demerol and Seconal were given for progressive labor which failed to respond to medication. Approximately five hours after admission contractions were at 4 minute intervals lasting 45 seconds and the cervix was 2 to 3 cm. dilated. Relaxin was started at 8 mg. equivalent per minute, and labor slowed immediately, to stop in approximately 6 hours. Treatment was continued at a lower rate for over 8 hours. This patient was discharged on the following day, and was delivered uneventfully of a 6 pound daughter at 37 weeks following spontaneous premature rupture of the membranes.

Through the courtesy of Dr. Allan C. Barnes and his staff at MacDonald House, University Hospitals, 2 primigravidas in normal labor were treated with intravenous relaxin. Strain gauge tokodynamometer tracings were made in continuity before, during, and after the administration of this drug (Figs. 5, 6, and 7). Ten milligrams per minute slowed labor within one hour, but 5 mg. per minute was not enough to maintain the stoppage produced by a single rapid injection of 100 mg. With adequate dosage disorganized contractions first appeared, and labor failed to progress. After complete arrest of labor, irregular contractions first reappeared, to be followed after a variable but brief interval by forceful, progressive labor.

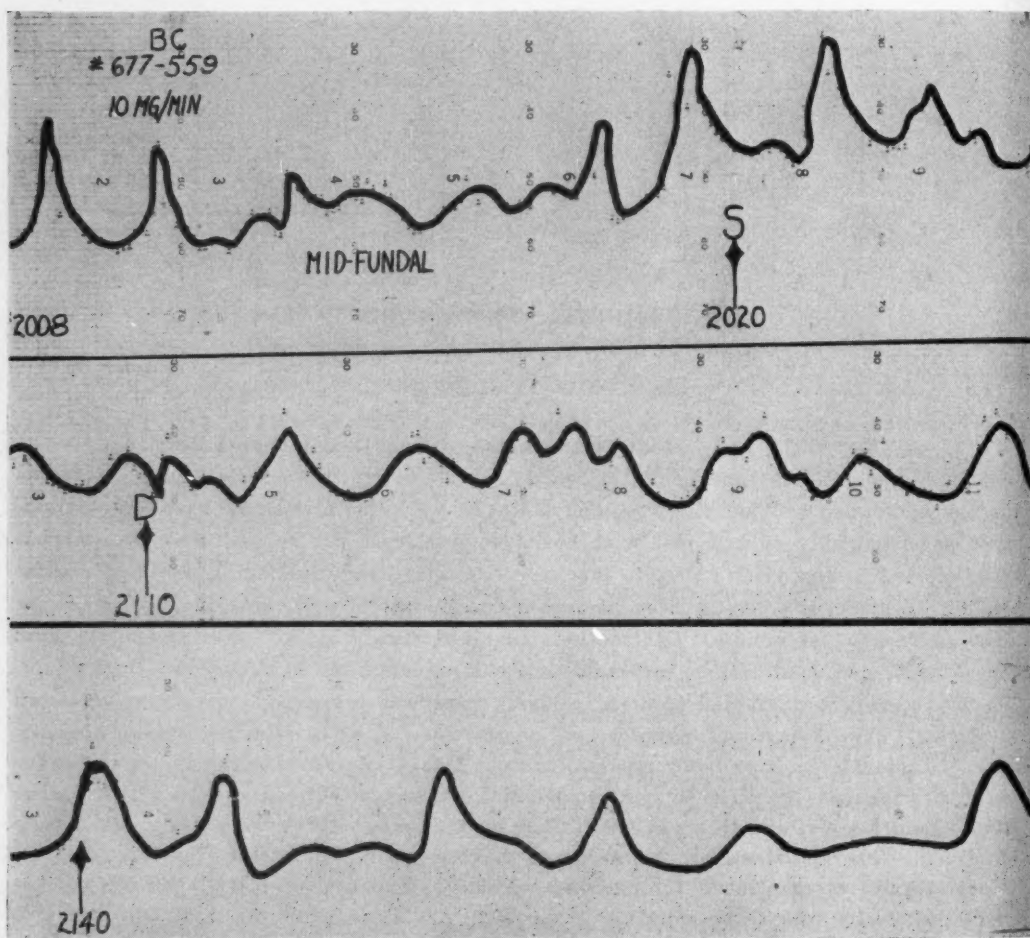


Fig. 5.—Segments of unipolar TKD tracings (U.H. No. 677559). Control portion, first line, has pattern of 1 to 2 weaker contractions interspersed between 3 to 4 minute strong contractions. Relaxin (10 mg. per minute) was added to intravenous glucose drip at S. Rhythm became irregular at 2055, but strong 4 to 5 minute contractions recurred within one-half hour of cessation of drip at D. At the onset of experiment, the cervix was 4 cm. dilated, and the vertex was at plus 1. There was no progress in labor until 2 hours after the completion of the relaxin drip. Delivery occurred at 2 A.M. the following morning.

Depot Relaxin.—

There is increasing evidence¹⁹ that the responses to relaxin may be modified by the addition of a depot material to slow the absorption and utilization. These changes may be species specific. Much experimentation is now being

done in an attempt to find the ideal "depot" for humans. Active labor was first controlled in 2 subjects in active labor at 25 weeks' gestation by intravenous relaxin. The first (V. H., No. 58652) was quiescent for 36 hours before depot gelatin-relaxin was administered, whereas the second (H. B., No. 58887) received the depot material synchronously with her intravenous medication. Each received 60 mg. followed in 2 hours by 40 mg. depot relaxin. The first subject was then given 50 mg. every 6 hours. Because of the disappearance of fetal heart tones, and the x-ray confirmation of fetal death (Buddha position), delivery was consummated on the fifth day. A 600 gram female infant that cried spontaneously was delivered by assisted breech extraction. She died on the twentieth day.

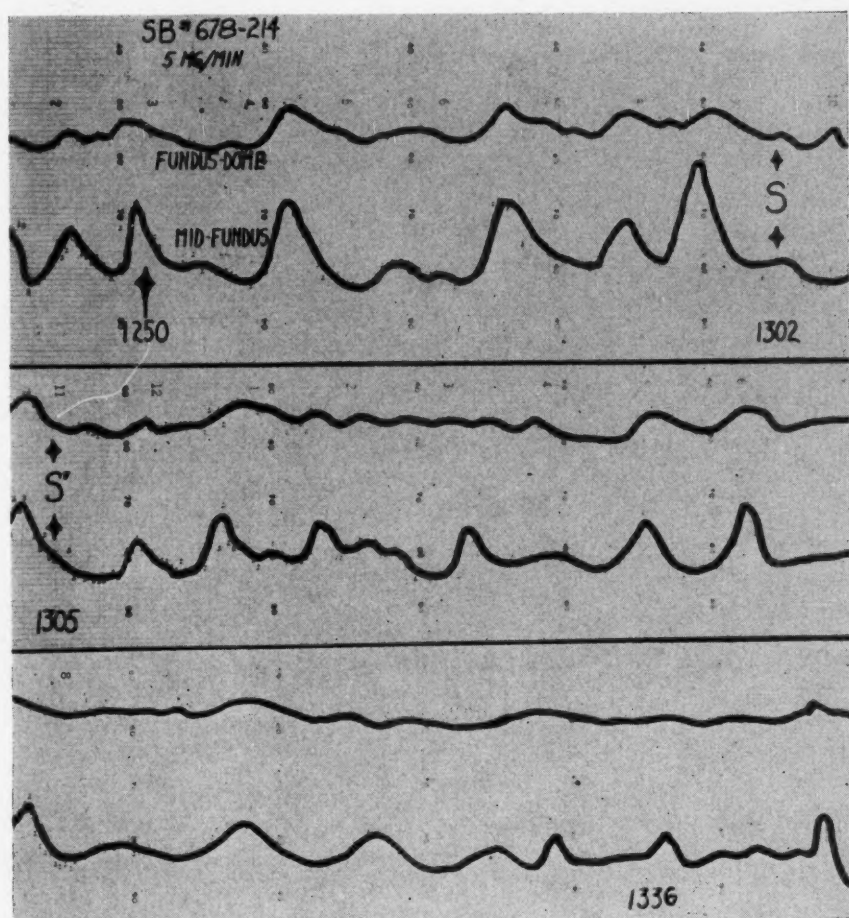


Fig. 6.—Bipolar TKD tracing, in continuity (U.H. No. 678214). Top graph shows strong contractions of normal labor pattern with rhythm of weaker contractions between the forceful ones. Relaxin (5 mg. per minute) was added to intravenous glucose drip at S, and at S' an additional 100 mg. of relaxin was injected relatively rapidly through the intravenous tubing into the subject. The resultant disorganization of labor is evidenced in the middle graph, whereas only ineffectual and weak contractions are seen in the third portion. Comparison of the first and third segments shows these marked differences. The patient slept, free of painful contractions from approximately 1315 to 1500, 1 hour and 45 minutes. There was no change in cervical dilatation (3 cm.) or descent (station 0) during the entire experiment.

The second subject received 400 mg. intravenous relaxin with her 100 mg. depot extract within the first 90 minutes. Contractions ceased within an hour, but the depot relaxin did not hold, or did not become effective soon

enough, as she delivered 3 hours after the start of therapy, 80 minutes after the cessation of the relaxin drip, and 40 minutes after the recurrence of labor. The infant did not survive. A similar experience, with surviving infants, was obtained in two additional patients at 34 and 35 weeks' gestation. Labor was slowed in each mother by intravenous relaxin, but the depository material could not hold the line. The apparent latent period in the development of an effective response to the gelatin-relaxin is quite variable. This increases the difficulties in the interpretation of results.

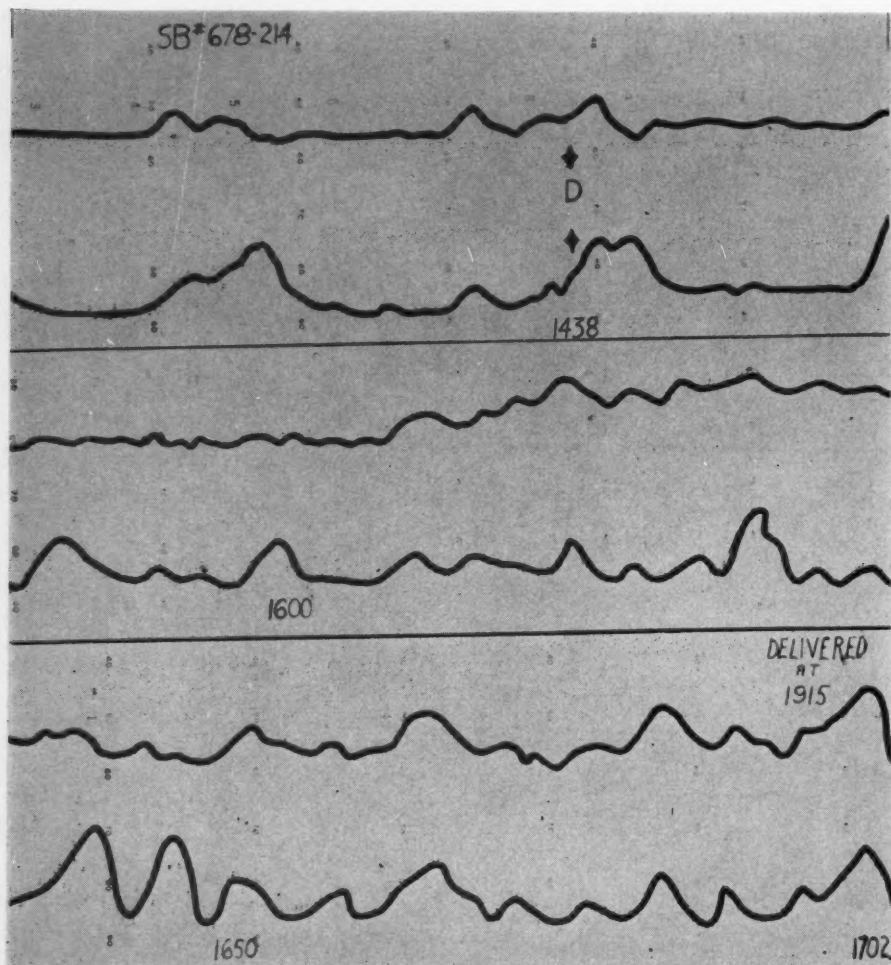


Fig. 7.—Bipolar TKD tracing, a segmental continuation of Fig. 6, showing early recurrence of contractions which aroused patient at the time of discontinuation of intravenous relaxin, D. The central chart, approximately one-half hour later, shows disorganized labor. These contractions were increasingly uncomfortable, but not effective. The last segment, 2 hours after cessation of relaxin therapy, demonstrates the return of strong contractions at $1\frac{1}{2}$ to 2 minute intervals, the general pattern being two weaker contractions followed by a forceful one. There was no evidence of progress in labor throughout the entire experiment which ended at 1702, 5 hours after its origin. Yet the patient shortly thereafter entered good labor, and delivered easily and rapidly within 2 hours.

Dysmenorrhea.—

Salutary effects have been obtained in 3 of 5 private patients with secondary dysmenorrhea associated with proved endometriosis and adenomyosis. Depot relaxin was used, 5,000 to 7,500 GPU at a single intragluteal injection

during the painful phase. These injections are painful, and this may be the cause of the good effects. No primary dysmenorrhea has been treated. No conclusions can be drawn from this small number.

Toxicity.—

At the present writing 78 subjects have received at least one dose of relaxin under our selected experimental conditions. Maximum dosage schedules have varied in time and amounts, from divided intramuscular injections of 75,000 GPU daily for 5 days each month for 6 months to 800 mg. active principle (approximately 120,000 GPU) intravenously within one hour. One subject has received 2,600 mg. within a 24 hour period by continuous intravenous drip, and another has received the same amount by discontinuous drip in a 48 hour period. One subject has received approximately 1,000 mg. by intravenous drip at the twenty-fifth week of gestation, which was repeated at 29 and 36 weeks. In no patient treated by us did any evidence of sensitivity develop. This includes the group in whom intravenous pyelograms were done twice in one week at monthly intervals for over six months.

Comment

In this experimental work on relaxin we have been confounded by the contradictory reports on the effects of this hormone. Our results differ from those of some investigators, and this may be because of the difference in relaxin supplies available, or tissue sensitivity and response, or only because we do not have a common definition of the terms we use. What is labor? I am sure that our definition differs from that of Abramson and Reid,² just as it does from that of those who have reported the results of the use of the Uterine Relaxing Factor. Even our tokodynamometer tracings lend themselves to variable interpretation. I cannot emphasize too strongly the work of Kliman and Greep¹⁹ who showed that guinea pig relaxing factor could be potentiated by changing its solubility, whereas the mouse factor could not, and thus apparently different products may only be different forms of the same one. At the present writing this drug is in the same status as the estrogens were in the early 1930's, when each estrogen had to be standardized by a different biologic technique, as even the addition of a new radical changed the physiologic response and dosage. We know what we have not accomplished as yet. We have not produced repeatable hormonal ureteral dilatation. We have not found a formula for the simplified production of satisfactory labor in the patient with the unripe cervix. We do know that we have produced an extreme softening of the cervix in many patients, and we have clinical evidence that relaxin can and does disturb the uterine rhythm of parturition, and in some patients is capable of completely stopping progressive labor. Since in most cases there is a delay of up to two hours in the original response to intravenous relaxin, it must be inferred that the action of relaxin is not direct, but is mediated by some as yet unknown mechanism. Once the response has occurred, however, it may be reproduced rapidly on the already primed organism provided too long a latent period has not intervened. In no case has there been any evidence of toxicity to or antigenicity from relaxin. More work must be done, on both the clinical and experimental levels. We hope to be able to report progress in this venture at a future meeting.

Summary

Seventy-eight patients and experimental subjects were treated by relaxin intramuscularly or intravenously. Nine were checked for ureteral dilatation and symphyseal separation. In one subject, minimal separation of the symphysis and elongation of the ureter was produced. These results could not be reproduced despite modifications of the dosage schedule. Five patients were treated for dysmenorrhea, but no conclusions can be drawn. Depot (repository gelatin) relaxin was used alone in 2 subjects, and in conjunction with solution relaxin in 4 additional ones. Injections are painful, and the latent period is apparently too great to be of value in the current research in the present state of our knowledge. As new depot material becomes available, with a more immediate and prolonged response, these problems should be reopened for further study.

The most gratifying results were in modifying labor. Intravenous and intramuscular relaxin was used on 15 patients in active labor. There is a latent period in the response of relaxin of approximately one to one and one-half hours regardless of the route of administration except when rapid intravenous medication is given in large quantities. We were able to modify and slow labor in all patients to whom adequate dosage could be given for over two hours preceding delivery. Depot relaxin, which could obviate the use of excessive quantities of this relatively unavailable hormone, has too great a latent period to be of value as yet.

A second favorable response which warrants further study is the definite softening of the cervix which occurred in almost all patients. This was noted to a moderate or more extensive degree in 30 of the 39 subjects studied for cervical softening. It was marked in those who failed to progress in active labor after the start of relaxin therapy. The apparent effacement and dilatation diagnosed by rectal examination were not always confirmed by vaginal examination. Yet several primigravidas went from 3 to 4 cm. dilatation to delivery within two to three hours after contractions recurred. Certain types of labor associated with disorganized contractions (inertia) responded with normal labor and rapid delivery. More work must be done in an attempt to find the key which will unlock this enigma of cervical softening, and its effect on induced labor. In no patient did relaxin interfere with the action of pituitary extract.

Conclusion

May we conclude with the remarks of Dr. Roy Greep¹⁵ who presided at a recent informal conference on relaxin. He reminded those present that relaxin is a most elusive hormone, and that at this stage of our knowledge, we should be careful that we do not develop either unwarranted optimism or pessimism as to its potentialities. We hope we have done neither.

We take this opportunity to thank the past and present Superintendents at Cleveland State Hospital, Drs. M. B. Gordon and W. L. Grover, respectively, for the permission to use their facilities, Dr. Allan C. Barnes and his staff at MacDonald House, University Hospitals, for their cooperation and assistance, and particularly Dr. Charles Hendricks for

his instruction in the interpretation of the tokodynamometer tracings. We also wish to express our appreciation to the cooperating departments at all the hospitals, and to the physicians who permitted us to use their patients as experimental subjects.

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Discussion

DR. C. PAUL HODGKINSON, Detroit, Mich.—The authors have demonstrated that parenteral use of relaxin is safe. We have concerned ourselves with a fibrinogen-platelet test for safety of drugs given intravenously. As preliminary observations, substances such as trypsin, incompatible blood, plasma expanders, and certain other drugs which produce occasional reactions cause fibrinogen and platelet depression in a way suggestive of thromboplastin influence. Relaxin,* 233 mg. diluted in 200 c.c. glucose solution, when tested in this manner failed to cause fibrinogen or platelet depression. Using these standards, our studies agree that this brand of relaxin is safe for human use.

The authors attempted to reproduce, in a measurable degree, through administration of relaxin in high dosage, clinical conditions observed during pregnancy which possibly are caused from endogenous relaxin. The main issue is to determine if the results by Eichner and his associates are results which can be accepted as having been caused by the pharmacological properties of the drug. In the matter of separation of the symphysis and dilatation and relaxation of the ureters, the answer is "no effect."

Softening of the cervix uteri at term is a matter difficult to evaluate, and its measurement is often a clinical guess. Dr. Eichner observed that relaxin-induced cervical softening

*Releasin, Warner-Chilcott Co., New York, N. Y.

did not necessarily lead to effacement, nor was there evidence that the administration of relaxin increased the success of induction. They observed that labor was of short duration and delivery often precipitous after administration of the hormone.

Our clinical impression of the cervix in late pregnancy, from observation of 20 relaxin-treated patients, largely corresponds with Dr. Eichner's. We, too, were impressed with the soft state of the cervix. We were impressed that the hormone did not increase the success of induction per se, but it did possibly produce a cervix more suitable for amniotomy. With the amnion ruptured, the uterine response to Pitocin was frequently vigorous and the duration of labor brief. Interference with postdelivery myometrial contraction did not result in uterine atony nor hemorrhage. In 26 nonpregnant patients, not primed with estrogen, cervical softening was not detected.

Our experience with efforts to diminish the myometrial contractions of true labor was not successful. Premature labor in 3 patients appeared to be shortened. Three other patients were discharged from the hospital undelivered. These results were construed as indicating rather poor ability to diagnose labor and not 50 per cent drug success. The experiences of the authors with cervical dystocia, cervical stenosis, and secondary uterine inertia were interesting and stimulating to further study. Reynolds, Harris, and Kaiser,¹ using the multichannel strain gauge tokodynamometer, showed that myometrial contractions of normal and abnormal labor could be inhibited and otherwise influenced by such subjective factors as the administration of a placebo pill, the assuagement of fear, and the administration of sedation. One would inquire, if, in the opinion of the authors, the "relaxin rest" might not have been influenced, to some degree, by the confidence-inspiring personalities of the able and experienced clinicians who were responsible for this interesting presentation.

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DR. EICHNER (Closing).—On the strain-gauge tokodynamometer what we did for control was this: The mechanism was set up after the intravenous injection was started. An injection of dextrose in water was used. The patient had the injection running at the time we made the proper attachments of the gauges; and at a somewhat later period, half an hour to an hour later, the relaxin was injected into the bottle. During this particular time on various occasions the patient did have an injection of saline or sugar into the tubing, so she knew that medication was being injected at various intervals, and she was not aware of when the relaxin was put into the bottle. We feel that is the best control we can get.

**RELATIVE ATONY OF MYOMETRIUM UNDERLYING THE
PLACENTAL SITE SECONDARY TO HIGH CORNUAL
IMPLANTATION—A MAJOR CAUSE OF
RETAINED PLACENTAS***

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PRIOR to the past decade careful obstetricians, fearing infection, avoided manual removal of retained placentas except as a last resort.²² My early obstetric education was thoroughly infused with these extremely conservative teachings. With the advent of antibiotics, however, many obstetricians, now fearing hemorrhage more than infection, manually remove retained placentas within fifteen to thirty minutes after delivery of the baby.²⁰ Clinical reports^{4, 14, 16} indicate that the danger of infection, following third-stage and postpartum intrauterine manipulations, is not so great as previously thought. In fact, antibiotics may not be necessary to protect such patients if aseptic technique is meticulous.⁸ The patient's safety is further enhanced by more readily available transfusions.²⁰

This evolution in the management of patients with retained placentas has exposed the third-stage uterus more frequently to inquisitive fingers. The following information stems from that fact.

Initial Observations

Several years ago I noted a series of similar findings during manual removal of retained placentas. These are best illustrated by brief case histories.

On March 16, 1949, Mrs. H. L., aged 19 years, gravida ii, para i, at term, in labor, was referred for delivery. An arcuate uterus was noted. The fetal buttocks were in the right horn. The left horn was bulbous and relatively flaccid during uterine contractions. The baby was delivered spontaneously after a five-hour labor. There was no bleeding in the third stage, but the placenta did not separate and so was delivered manually fifteen minutes later (Fig. 1). At this time it was noted with interest that the *musculature* under the *placental site* in the *left horn* was exceedingly thin and atonic, whereas the contracted musculature of the rest of the uterus was considerably thicker.

On May 8, 1949, Mrs. H. H., aged 35 years, gravida ii, para 0, at term, in labor, was referred for delivery. (Two years previously, during curettage for incomplete abortion, a bicornate uterus had been discovered.) Now the left uterine cornu was replaced by a 25 by 25 cm., balloonlike, compressible, atonic area. Following an easy four-hour labor and spontaneous delivery of the baby, the placenta separated only partially. Therefore, it was removed manually after twenty minutes, and, again, a very thin musculature was found under the placental site high in the left horn, though the uterus was otherwise firmly contracted.

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On July 7, 1950, Mrs. L. P., aged 32 years, gravida iii, para ii, three weeks from term, in labor, was referred for delivery. Twins were noted, the first in the cephalic presentation and the second in transverse presentation. Likewise, there was a large, soft, non-contractile region in the right horn of the uterus. After five hours and fifteen minutes of labor the first twin was delivered spontaneously, and the second twin was delivered by version and extraction. With the patient awake we waited thirty minutes for separation of the placenta and then delivered it manually. The placental site was found to be high in the right horn of the uterus, and the musculature under it was extremely thin and flaccid.



Fig. 1.

The recurrence of this phenomenon—in association with retained placenta was most intriguing. A definite effort was made to examine for it in those instances where the third stage of labor lasted more than fifteen minutes. Usually the findings were as follows: the placenta was primarily located in the cornual region. The myometrium under it was very thin and quite atonic. To this relatively atonic area the placenta remained attached. However, manual separation was not difficult; there were no obstructing fibers or bands of tissue holding the placenta. The remaining musculature of the uterus sometimes retracted quite firmly around and below the placenta, producing what might be considered to be a constriction ring. Even after manual removal of the placenta the thin musculature which had been under the placental site would remain obviously atonic and markedly thinner than the remaining uterine wall. Sometimes the patient would be allowed to awaken almost to full consciousness before the examining hand was withdrawn; yet some degree of thinness and atony of cornual placental site musculature still was palpable.

Though some cornually implanted retained placentas were found in arcuate and bicornate uteri, more occurred in otherwise perfectly normal uteri.

These findings are most logically explained by the following sequence: Implantation of the fertilized ovum probably occurs high in the uterine horn, but not quite high enough to become an interstitial pregnancy.¹⁷ At term

such a high cornual implantation probably results in a relatively thin, relatively atonic musculature under the placental site which does not have sufficient power to shear off the placenta before contraction and retraction of the remaining uterus form a barrier to normal separation and delivery.

This idea was kept in mind merely as a theory, but careful examinations were made and records were kept on those few patients in whom manual delivery of the placenta was necessary until Sept. 10, 1954.

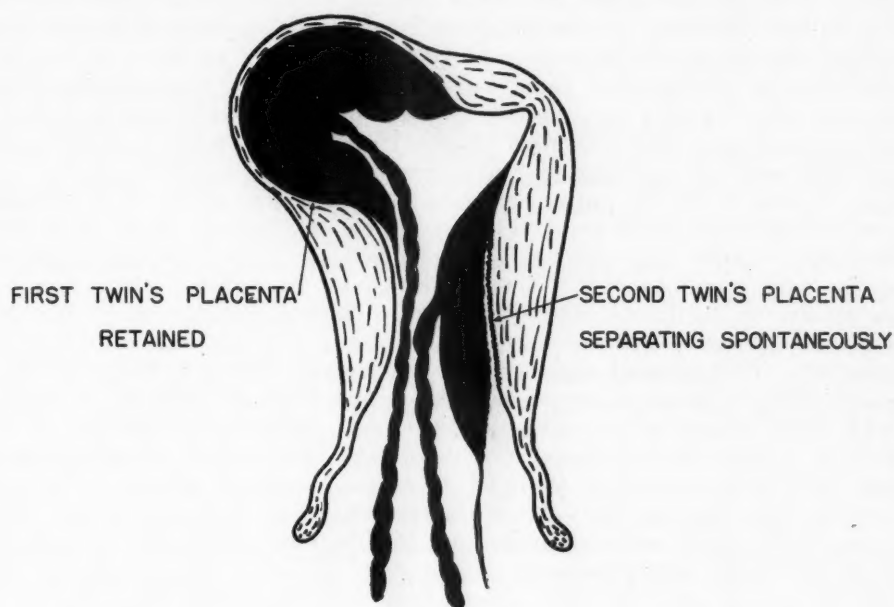


Fig. 2.

On this date Mrs. J. H., aged 26 years, gravida iv, para iii, at term, in labor, entered the hospital. After an easy twenty-four-hour labor, her twins were delivered spontaneously (Fig. 2). A placenta which had nourished the *second* twin separated spontaneously from the left anterior uterine wall two minutes after the end of the second stage. The placenta which had nourished the *first* twin did not separate, however. Therefore, after twenty minutes, the retained placenta was removed manually. It was found implanted in the right horn of the uterus with a very thin, flaccid, underlying musculature. Manual examination revealed the musculature under the spontaneously separating placenta to be essentially the same thickness as the remaining walls of the uterus. However, the musculature under the manually removed placenta remained quite thin and flaccid as long as the examining hand remained in the uterus.

This patient's third stage truly constituted a single, controlled experiment which seemed to substantiate the theory presented above. Thus, the placenta of the second twin which separated so quickly and spontaneously, and under which the musculature was so firm and thick, acted as a control. Conversely, the placenta of the first twin, which had to be removed manually, and under which the musculature was so thin and flaccid, seemed to demonstrate the effect of high cornual implantation.

This interesting observation stimulated me to set up clinical experiments to test this theory of the cause of many retained placentas. Before describing

these experiments, however, it is necessary to mention a few of our procedures during labor and delivery, because separation of the placenta is subject to variations in uterine motility, and because uterine motility is so easily modified by anesthesia, analgesia, and delivery techniques.

Delivery Techniques

We use relatively light analgesia. A large majority of our patients are delivered spontaneously, and receive a minute or two of light gas anesthesia during actual delivery of the baby, following which they are immediately awakened during the third stage. Only after delivery of the placenta do we anesthetize the patient for repair of the episiotomy. Sometimes pudendal blocks are used. For a forceps delivery we attempt never to anesthetize the patient more deeply than the first plane of the third anesthesia stage, and we immediately stop all anesthesia and replace it with straight oxygen as soon as it is obvious that the patient will be delivered within the next minute or two, so that most patients are awake within two to four minutes after the end of the second stage. Patients usually receive 1 c.c. of Pitocin intramuscularly when the baby's shoulders are being delivered. We try to deliver the babies rather slowly to facilitate retraction of the uterine musculature. We do not massage the uterus or use the Credé maneuver nor do we wait a long time for classical signs of placental separation. We merely utilize a modified Brandt³ maneuver every minute or two during the third stage to evaluate uterine tone and to test for placental separation. When the placenta has separated we express it by gentle fundal pressure.⁵ With this combination of techniques our *average duration of the third stage is five minutes and ten seconds*. We suspect that many placentas separate much faster than this,^{5, 6} but that the average duration of the third stage is prolonged to this length because of the time we often devote to the newborn baby.

Methods and Results

This problem was investigated by the use of three methods:

1. The records from fifteen hundred private patients, delivered by me, dating from January, 1949, through April, 1955, were examined (Table I). Among these, the retained placentas of 62 patients *were removed manually*. *Forty-five of these manually removed placentas* were found partially or completely implanted *high in the cornual portion of the uterus*, and in each instance the *musculature* underlying the placental site was *quite thin and relatively atonic*.

Three manually removed placentas were located in the lower uterine segment and were associated with previable delivery and partial placenta previa. Here, a relative atony of the placental site may have caused retention, and in one instance where the placenta encroached upon the cervix, an inadequate decidua may have contributed to retention. In one instance the center of the placenta was attached to the anterior uterine wall directly over a 6 cm. submucous fibromyoma. It is interesting that this placenta was entirely separated except for that surface attached directly over the submucous tumor. In this instance either total atony of a portion of the placental site or inadequate decidua of that region caused retention. Manual separation was so easy and the cleavage plane so neat that it was difficult to blame an inadequate decidua.¹⁶ Eight placentas were removed manually following operative deliveries such as breech extractions and midforceps. In each instance uterine atony and heavy third-stage bleeding forced manual removal. In most of these the depth

of anesthesia during the second and third stages contributed heavily to the uterine atony. Six of these 8 instances involving atony of the entire uterus occurred prior to 1951. Since then we have emphasized the importance of avoiding deep anesthesia during the third stage, and this problem seldom recurs.

TABLE I. APPARENT CAUSES OF PLACENTAL RETENTION
 1,500 DELIVERIES

| | |
|--|------------|
| Manual removal of retained placentas | 62 |
| Cornual implantation with relative atony of placental site | 45 (72.6%) |
| Other atony | 12 (19.3%) |
| a. Partial placenta previa, previable delivery, atony of lower uterine segment. Inadequate decidua? | 3 |
| b. Placenta implanted over submucous fibromyoma, local atony. Inadequate decidua? | 1 |
| c. Breech and midforceps deliveries. Deeper anesthesia in third stage. Generalized uterine atony. Bleeding | 8 |
| Other causes | 5 (8.1%) |
| a. Hemolytic disease. Stillbirth. Edematous 5 pound placenta | 1 |
| b. Bidiscoid placenta | 1 |
| c. Records inadequate to evaluate causes of retention | 3 |

2. This finding of thinness and relative atony under cornually implanted placentas was discussed with various obstetricians. Opinions were expressed that myometrium underlying the placental site is always thinner than the remaining musculature of the uterus. To evaluate the relative thickness of musculature under various placental sites the following clinical experiment was initiated in October, 1954, and continued through one hundred consecutive vaginal deliveries of my patients. Immediately after delivery of the baby, while an assistant held the baby to one side, the inside of the uterus was examined to determine exactly where the placenta was located. This took but a few seconds, and thereafter the patient was handled exactly as we ordinarily care for patients, until the end of the third stage. Then, immediately after delivery of the placenta, the placental site was examined, and the thickness of the underlying musculature was estimated in millimeters.

Of course, this estimate was based only on bimanual palpation and cannot be considered an exact measurement. Without being too facetious, however, it may be said that a fair portion of an obstetrician and gynecologist's diagnostic acumen derives from his ability to judge distance, space, and texture reasonably accurately by his tactile senses. Certainly, there is some error in these estimations of thickness of the uterine musculature, but since all of the measurements were made by the same individual it is very likely that the error of estimation is all in the same direction. Therefore, since we are not so much interested in exact thickness as in relative thickness of different placental sites, we submit that this method of experimentation is not so inexact as it might seem on first thought.

Recently it was possible for me to check my estimation of thickness according to tactile sensation by direct observation at cesarean section.

On March 29, 1955, Mrs. G. T., aged 17 years, gravida i, para 0, at term, entered the hospital in labor. An android pelvis with some narrowing of the midplane had been noted previously. The baby was in breech presentation. After twenty-one hours of incoordinate labor the cervix was approximately 5 cm. dilated, and both of the baby's feet were in the vagina. A low cervical cesarean section was performed. It is our habit to give oxytocics after delivery of the baby at cesarean section and wait for spontaneous separation of the placenta. This placenta did not separate spontaneously, however, and so was removed

manually after five minutes. It was found to be implanted very high in the right horn of the uterus, and the musculature underlying it was estimated to be no more than 2 or 3 mm. in thickness. After removal of the placenta the entire uterus was delivered through the abdominal incision, for the first time, and the thickness of the myometrium at the placental site was re-evaluated both by palpation and by observation (Fig. 3). By this method we were able to check the accuracy of our tactile sense in estimating thickness, and in this instance we found it to be very accurate indeed. The musculature of the cornual placental site was so very thin as to raise a serious doubt concerning its ability to withstand a strong uterine contraction without being ruptured. Likewise, we discovered that this patient had a unilateral right uterus within which the pregnancy developed, and to which was attached an incompletely developed left uterus.

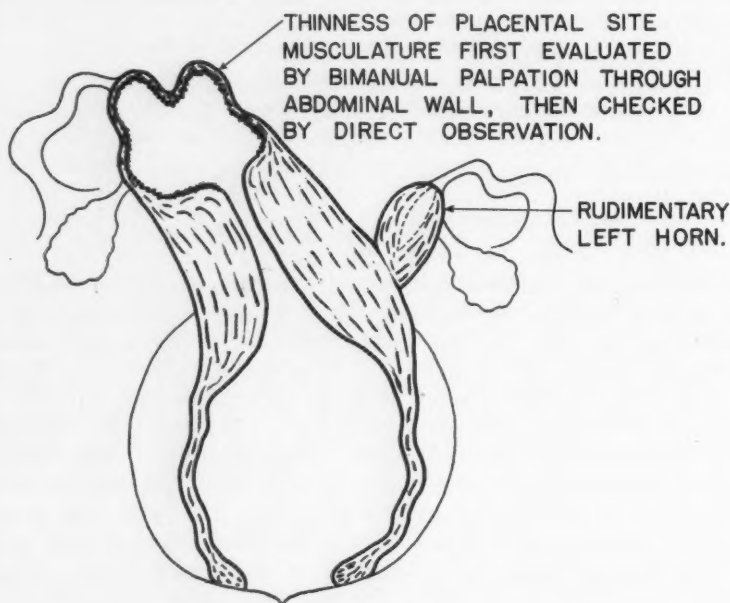


Fig. 3.

Of these 100 placental sites which were examined, 47 placentas were attached to the anterior uterine wall; 42 to the posterior uterine wall; 4 directly in the fundus; 2 high in the right horn; and 5 high in the left horn. Of the 93 which were attached primarily to the anterior and posterior walls and in the mid-portion of the fundus (Table II) the average estimated thickness of the musculature under the placental site immediately after delivery of the placenta was 15 mm. These placentas separated spontaneously and were delivered by early expression. The remaining 7 placentas were removed manually after an average wait of sixteen minutes. These 7 placentas had major locations in either the right or left horn of the uterus. The average estimated thickness of the musculature under the placental sites was 5 mm. In all these latter instances the musculature at the placental site was atonic when compared with the remaining musculature of the uterus.

3. There is a theoretical objection to the experiment outlined above. The objection is this: Starting with the onset of labor and continuing more rapidly near the end of the second stage, the uterine musculature changes its shape and size. Possibly this contraction and retraction of the myometrium which produces the shearing off of a spontaneously separating placenta would thicken the musculature of the placental site, whereas it might be thinner if the pla-

centa were removed manually. In order to evaluate this possibility we manually removed placentas from 25 successive Rh-positive mothers immediately after delivery of the baby, with the exception of only a very few cases where the baby required continuing attention during this particular interval. In those cases in which we were occupied with the baby for more than two minutes we did not attempt manual removal. In this group of 25 patients the average duration of the third stage was just less than two minutes. During the manual removal we estimated the thickness of the musculature underlying the placental site, and then immediately estimated the thickness of the opposite wall of the uterus. When the placental site was in the fundus or in the cornual region we also estimated the thickness of both anterior and posterior walls of the uterus. It is true that the uterus retracts so rapidly during the delivery of a baby that these estimates are not true estimates of the thickness of the placental sites with a baby in utero. Again, their worth is not as true measurements, but as relative measurements.

Eight placentas were attached to the anterior uterine wall. The estimated thickness of underlying musculature averaged 13 mm.; the estimated thickness of the posterior walls averaged 15 mm.

Twelve placentas were attached to the posterior uterine walls. The estimated thickness of underlying musculature averaged 15 mm.; the estimated thickness of anterior walls averaged 16 mm.

Four placentas were attached in the fundus. The estimated thickness of underlying musculature averaged 8 mm.; the estimated thickness of the anterior walls averaged 17 mm.; and the estimated thickness of the posterior walls averaged 16 mm.

One placenta was found attached high in the left horn of the uterus. It is very likely that this placenta would have required manual removal anyway. The musculature underneath this placental site was estimated to be 6 mm. thick. In this uterus the musculature of both the anterior and posterior walls was estimated to be 20 mm. thick.

TABLE II. RELATIVE THICKNESS OF MUSCULATURE UNDER RESPECTIVE PLACENTAL SITES

| NUMBER EXAMINED | LOCATIONS | SEPARATION | AVERAGE DURATION OF THIRD STAGE | AVERAGE OF ESTIMATED THICKNESS OF MUSCULATURE |
|-----------------|---|----------------|---------------------------------|---|
| 93 | Anterior wall Posterior wall Fundus | Spontaneous | 5 minutes, 10 seconds | 15 mm. |
| 7 | Right horn Left horn | Manual removal | 16 minutes | 5 mm. |

Comment

These investigations have taught us that the uterus, in the semiretracted stage immediately after delivery of the baby (Fig. 4), has fairly thick anterior and posterior walls, a slightly thinner lateral wall where the anterior and posterior walls come together, a considerably thinner fundal wall at the apex of the anterior and posterior walls, and extremely thin areas, palpable in almost every uterus, near the uterotubal junctions.¹⁶ Likewise, it was evident that while the musculature under the placental site tends to be slightly thinner than the opposite wall of the same uterus, this difference was not so great as to modify the shearing action of myometrial retraction⁹ unless the placenta was located in a relatively weaker, atonic portion of the uterus, namely, the

cornual or fundal portion. Placentas attached on the anterior and posterior walls of the uterus were easy to remove manually, placentas attached near the fundus were somewhat more difficult to remove, and placentas attached in the fundal and cornual portions of the uterus became increasingly more difficult to remove, apparently in direct proportion to the height of their implantations. This difficulty in removing cornual and fundal placentas was due primarily to the flaccidity of the underlying musculature,¹² and in some instances to the secondary myometrial retraction around and below the placenta. In no instance did this retraction occur below a placenta normally implanted on the anterior or posterior wall of the uterus. It was observed only when the placenta was implanted high in the fundus or horn, and then only after several minutes in the third stage. Just as the phenomenon of menstruation is a secondary result of the ovarian-endometrial relationship, so this myometrial retraction appears to be a secondary result of retention of a placenta high in the uterus. The basic cause of the retention of the placenta appears to be inability of the relatively atonic placental-site myometrium to shear off the placenta.

Rarely is a placenta confined to one horn of the uterus. Should its major attachment be in the cornual region, one or more borders will usually extend out over the fundus or the anterior or posterior uterine wall. In these instances those portions of the placenta which are over strongly contracting myometrium will be found to have separated prior to manual removal whereas those portions overlying flaccid, thin myometrium will usually be found still attached thereto. If the major portion of a placenta is attached over strongly contracting myometrium, and only a small portion is attached over relatively atonic myometrium in the horns or the fundus, then the placenta will usually separate spontaneously, but the third stage will be prolonged from five to fifteen or twenty minutes, and delivery of the placenta will be more difficult than average.

Delivery techniques and anesthesia have an effect upon uterine contractions and thus modify the duration of the third stage. We think it is significant that the average duration of the third stage in patients under our management whose placentas separate spontaneously is five minutes and ten seconds. This means that if the Brandt maneuver,³ repeated occasionally, does not demonstrate separation of the placenta some time within five or ten minutes after the delivery of the baby, we examine for a marked asymmetry of the uterine fundus, which will usually be evident if there is a cornually implanted placenta. This marked bulging of one horn during a third-stage uterine contraction is often the first physical sign of a cornually implanted placenta, though occasionally uterine asymmetry may make one suspect this phenomenon earlier in labor or, rarely, prior to labor.

As a rule we will wait at least fifteen minutes, but seldom more than thirty minutes, after delivery of the baby, before removing a retained placenta. Occasionally we have removed a placenta manually which was largely separated, leaving only a small portion still attached high in the uterine horn. Certainly, by a process of gradual retraction, the uterus would eventually shear off some of these, but in present-day obstetrics we do not feel that it is wise to

wait an extended period of time for this to happen. To wait beyond a reasonable time is to invite continuing blood loss. Also, the longer a mother's legs remain up in stirrups the more frequent and severe will be postpartum thrombophlebitis, but we prefer not to break sterile technique by lowering legs during a third stage with retained placenta, because valuable time would be lost if sudden hemorrhage occurred. In addition, it has been suggested that difficult delivery of such cornually implanted placentas by early expression or Credé maneuvers may be the beginning of inversion of the uterus.¹²

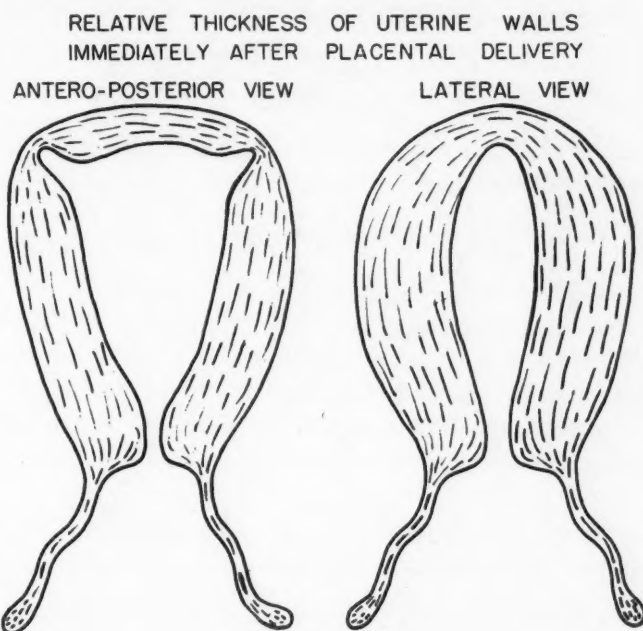


Fig. 4.

In general, our observations indicate that placentas attached to the anterior and posterior walls will separate rapidly and cleanly, and will almost never require manual removal. Conversely, the higher the placental attachment is in the fundus and horns, the less myometrial contractility will be present under the placental site, the longer the third stage will tend to be, and the more placentas will require manual removal because of retention.

It has been reported that manual removal of the placenta is more frequently necessary in women who have congenital anomalies of the uterus.^{1, 19} In our group of 62 women who required manual removal of the placenta there were 5 who had either arcuate, bicornate, or unilateral uteri. In each instance the placenta was implanted high in the uterine horn.

Concerning more unusual anomalies, the literature is confusing with relation to the terms *uterine diverticula* and *sacculation of the uterus*.^{2, 7, 13, 15, 18, 21, 24} In general, however, a diverticulum is considered to be an outpouching with a narrow neck, whereas sacculation of the uterus is considered to be a diffuse, balloonlike bulging of some portion thereof.¹⁰ It is entirely conceivable that a placenta implanted high in the horn, producing a large, soft, flaccid, balloon-

like bulging during first- and second-stage uterine contractions, as previously described, might be confused with a sacculation of the uterus. Probably it is a matter of definition. The cornually implanted placenta can produce diffuse bulging only in the involved uterine horn. Conversely, sacculation can occur almost anywhere in the uterine wall.

We have observed one instance of uterine asymmetry which probably should be classified as sacculation of the uterus.

SACCULATION OF RIGHT UTERINE WALL

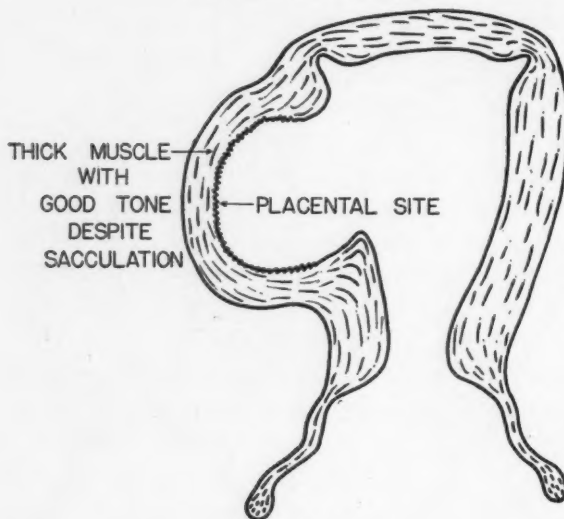


Fig. 5.

Mrs. J. Y., aged 36 years, gravida i, para 0, had much cramping and irregular spotting bleeding during the first five months of her pregnancy. A persistent tender bulging of the right side of the uterus was noted after the third month of pregnancy. Premature spontaneous leakage of amniotic fluid was first noticed late in the fifth month of pregnancy. This continued until delivery. Labor finally started spontaneously, and the patient was delivered of a 5 pound healthy infant four weeks prior to her expected term date. After delivery of the baby the asymmetrical bulging on the right side of the uterus remained (Fig. 5). This sacculation contained the placenta, which was expressed with only moderate difficulty after an essentially spontaneous separation seventeen minutes after delivery of the baby. Immediate postpartum examination showed the sacculation to be on the side wall of the uterus considerably below the right horn, and it was found that the musculature underlying the placental site was of approximately the same thickness as the musculature of the other uterine walls. This was not a cornual implantation of the placenta. It was probably a true sacculation of the right wall of the uterus, containing the placenta, but with sufficient thickness and tone of the myometrium to shear off the placenta during the third stage. No gross uterine anomaly could be palpated during bimanual examination two months post partum.

Among the 62 manual removals of the placenta, 12 were performed on 5 women. All 12 placentas were cornually implanted. Two women required 3 manual removals of the placenta, and 3 women required 2. All 5 had other pregnancies during which the placenta separated spontaneously. In each of these 5 patients each uterine horn has been involved at least once. There is no

note concerning uterine inertia in any of their labors except one dealing with a twin pregnancy. Some of these uteri have shown evidence of moderate difficulty in separating placentas during other pregnancies. This small group probably consists of women in whom the blastocyst tends more frequently to implant high in the horn of the uterus, predisposing to atony under the placental site and often requiring manual removal of the placenta. In general, it is thought that the fertilized ovum seldom implants in the cornual portion of the uterus because the decidual reaction is less pronounced there.¹¹ Perhaps this group of 5 women are exceptions to this general rule in that they produce good decidual reactions of the endometrium in the uterine horns.

Summary

1. During fifteen hundred deliveries it was necessary to remove the placenta manually 62 times. Of these retained placentas, 72.6 per cent were found to be implanted in the cornual portion of the uterus. Musculature under these placental sites was unusually thin and relatively atonic.

2. During one hundred consecutive deliveries the placenta was located by intrauterine palpation immediately after the second stage and the thickness and tone of musculature underlying the placental site were estimated by bimanual palpation immediately after the third stage. Musculature underlying cornual placental sites was relatively atonic and the average thickness was estimated to be one-third that of the firm musculature underlying all other placental sites.

3. Twenty-five placentas were manually removed immediately after delivery of the baby, and the thickness and tone of musculature underlying respective placental sites were estimated in relation to the same characteristics of the other uterine walls. The musculature of placental sites on the anterior and posterior walls was almost as thick and firm as the other walls of the same uteri. Placental site musculature in the fundus was somewhat thinner and softer. Placental site musculature in the cornua was obviously thinner and relatively atonic.

4. The evidence indicates that the primary cause of retention of many placentas is a relative atony of the musculature underlying placentas implanted high in the cornual region. Constriction below such placentas is due to the normal third-stage retraction, and should be considered more a result of placental retention than a cause of it.

5. Palpable asymmetrical bulging of a uterine horn during a prolonged third stage should lead the obstetrician to suspect this phenomenon as the cause of retention. Occasionally a cornually implanted placenta may be suspected during labor when one cornu is bulbous and contracts poorly.

Conclusion

A placenta which is implanted high in the uterus, particularly in a cornu, has a thin underlying myometrium with poor tone and will separate slowly or not at all. This is a major cause of retained placentas.

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Discussion

DR. SAMUEL D. SOULE, St. Louis, Mo.—Pregnancy associated with congenital abnormalities of the reproductive tract is associated with a higher incidence of retained or adherent placenta and a relatively frequent need for manual removal. It is also textbook teaching that pregnancy in the poorly developed horn of a congenitally malformed uterus predisposes to uterine rupture. This is understandable on the basis of poor muscular development in the rudimentary horn.

The anatomic developmental abnormalities of such women who do become pregnant are most likely to be mild to moderate, and to a substantial degree such defects are cornual. Thus, if the author's cornual implantations and cornual retentions were uniformly associated with palpable evidence of congenital malformation the conclusions would be more readily accepted. However, the musculature of a normal uterus presents no potential muscular defects in the cornu which would predispose to flaccid atony in this area when the placenta does implant. I should like to ask Dr. Ranney whether he ever notes thinning in the cornu when the placenta is normally implanted on the anterior or posterior wall of the uterus.

During the past two years there have been 12 pregnant patients with congenital defects of the uterus seen at the St. Louis Maternity Hospital. Three of these 12 had retained placentas. The site of implantation is not noted. In this same period of time 89 retained placentas were noted. Thus, about 3.3 per cent of retained placentas were associated with congenital abnormalities of the uterus and 25 per cent of the congenital abnormalities with retained placentas. These figures are mentioned without intrauterine palpation follow-up on the potential assumption that most of these patients statistically might present fundal or cornual defects.

Should cornual thinning be a factor in retention or adherence, might not one anticipate a greater degree of rupture in such patients as have implantation in this area? Spontaneous rupture of the uterus is a rare complication, however, except as noted previously when associated with the poor musculature of a rudimentary horn.

Relative atony of the myometrium underlying the placental site secondary to high cornual implantation as a major cause of retained placenta has been suggested by Dr. Ranney as an etiological factor. This suggestion must be given consideration. Independent investigations should be made to weigh these observations.

The 89 retained placentas noted in 1953-1954 at the St. Louis Maternity Hospital represent some 9,000 deliveries. This incidence of approximately 1 per cent is essentially the same as that reported by Eastman. The author's incidence of 4 per cent indicates a greater freedom with this intrauterine manipulation.

Whether one arbitrarily waits for 15 minutes or for one hour, the principle is that the uterus should be explored within some reasonable time after fetal extraction. Today, the safety of such intrauterine exploration is generally accepted. Having seen a maternal death due to a too-late diagnosis of placenta accreta, I too speak for arbitrary manual exploration of the uterus when the placenta is not expelled or expressed promptly.

DR. RANNEY (Closing).—Dr. Soule asked one question concerning whether or not I have found a thinning in the region of the cornual portion of the uterus in women who have apparently normal uteri and normal implantations on the posterior and anterior walls. As a matter of fact, I think I have noticed that quite regularly, not in every uterus but in approximately 75 per cent during the 25 experimental manual removals that were done.

If one examines carefully, a finger or two fingers can be introduced well up into the horn of the uterus where the myometrium is quite a good deal thinner than the remaining uterine musculature.

SOME OBSTETRIC FACTORS IN Rh ISOIMMUNIZATION*

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ERYTHROBLASTOSIS fetalis or hemolytic disease confronts the obstetrician and the pediatrician not infrequently. From the obstetric standpoint, little advancement has been made in treating this disease, but with a better understanding of the pathologic processes within the child and subsequently the perfection and timing of exchange transfusion, an increasing number of these infants are being saved.²² The ideal of any treatment, however, prevention, is far from being reached.

As yet, the explanation of the mechanism of maternal sensitization is still dependent on theory and little has been added since the basic chain of events was first proposed by Darrow² in 1938, and then clarified and related to the Rh factor by Levine⁹ in 1941. Simply stated, an Rh-negative mother is sensitized by the antigen in Rh-positive blood with the production of antibodies. These in turn traverse the placental barrier and may affect the red blood cells of an Rh-positive fetus in such a way as to cause hemolytic disease and occasionally death.

It is easy to understand how injection of relatively large amounts of Rh-positive blood into the Rh-negative mother would sensitize her. The phenomenon has been well established by many observers. It is also easy to comprehend how mixing of the bloods of an Rh-positive fetus and an Rh-negative mother would isoimmunize the mother. It has been said that this incident occurs through placental hematomas or red infarcts.⁶ To substantiate this theory, these infarcts are said by some to contain fetal blood.⁶ Others, however, have shown them to be composed of maternal blood.¹⁷ One observer showed that these infarcts, or breaks in the placental barriers, occurred no more frequently in erythroblastosis than in normal pregnancies and that microscopic examination of these hematomas in both erythroblastosis and normal placentas showed them to be the same.⁸ The proponents of the theory of sensitization through placental hematomas also claim that there are more infarcts due to traumatic obstetric procedures. They have not produced solid evidence of this, however.^{4, 16, 21}

It is stated that abortion, spontaneous, induced, or completed by dilatation and curettage, cesarean section, manual removal of the placenta, induced labor, etc., are more frequent in the obstetric histories of immunized women.

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Some maintain that the birth itself, whether spontaneous or induced, may cause isoimmunization.²¹ From a review of the literature, it appears that it usually takes a traumatic obstetric procedure or incompatible transfusion to immunize an Rh-negative mother.

Gainey and his associates⁴ were the first to offer any statistical evidence in relation to this subject. It was their definite feeling that obstetric trauma of one sort or another was a definite factor in isoimmunization of the Rh-negative mothers.

Material

We have taken 660 Rh-negative women from private practice and 103 patients from the Ripley Memorial Hospital, a total of 763 Rh-negative mothers. An analysis of these patients follows the usual pattern in relation to the number of pregnancies per patient, percentage of abortions, survival of affected and unaffected infants, etc. (Table I).

TABLE I. OBSTETRIC HISTORY

| | CONTROL | | STUDY | |
|---|---------|------|-------|------|
| | NO. | % | NO. | % |
| No. patients | 66 | | 24 | |
| No. pregnancies per patient | 2.6 | | 3.6 | |
| Survival all conceptions | | 91.3 | | 82.6 |
| Survival viable fetuses | | 98.7 | | 86.6 |
| Abortions | | 7.5 | | 4.6 |
| Fetal survival in pregnancies following sensitization | | 0 | | 72.0 |

There were 24 isoimmunized Rh-negative mothers, all but one of whom have borne proved erythroblastotic infants. The one exception had Rh anti-serum with saline titers of 1:1,000 after delivery of her firstborn, and a 1:4 albumin titer just before delivery of an Rh-negative infant. As mentioned previously, in an investigation of this type, it is important to know the immunization of these patients. This is ultimately possible only by finding erythroblastosis in the children. Our control group consists of 66 Rh-negative mothers, all of whose children were Rh positive, this being proved either by finding the father homozygous Rh positive or the patient having delivered two or more Rh-positive infants. The remaining patients of this total had at least one of the following, and, therefore, could not be used in this study: (1) Rh-negative husband, (2) only one child, or (3) babies were not typed and/or zygosity of father was not determined.

Study Group

There were 4 instances of an abnormal obstetric experience in the group of 24 isoimmunized mothers. The remaining 20 were delivered by outlet forceps or spontaneous delivery. Briefly, the histories of these 4 patients are as follows:

1. Mrs. J. P., No. 11656. The husband was homozygous. A cesarean section was performed for the first baby for a breech with inertia. No postpartum titer, was obtained and no titer was determined at 39 weeks during the second pregnancy. A stillborn erythroblastotic infant was delivered, and three weeks post partum the albumin titer was 1:512.

2. Mrs. G. P., No. 7341. The husband was heterozygous. The first pregnancy resulted in a normal baby, Rh group unknown. A spontaneous abortion occurred in the

first trimester of the second pregnancy and no titer was determined. The next child had erythroblastosis and the mother had antepartum titers.

3. Mrs. P. D., No. 13316. The husband was heterozygous. She had had two normal pregnancies with infants of unknown blood type. The third pregnancy was a spontaneous abortion with no titer determination. The third living child had erythroblastosis but there were no antepartum or postpartum titer determinations.

4. Mrs. M. S., No. 30832. The husband was homozygous. She had had four normal children of unknown blood type and then two spontaneous abortions. The seventh pregnancy resulted in the birth of an erythroblastotic infant that lived because of an exchange transfusion.

Thus, 4 of 24, or 17 per cent of our isoimmunized mothers, have had an abnormal obstetric incident.

Control Group

In the control group, 29 of 66 patients, or 44 per cent, had some obstetric incident other than simple delivery. All of these procedures at one time or another have been mentioned as a factor in isoimmunization. They are tabulated along with the frequency of occurrence in Table II.

TABLE II. OBSTETRICAL TRAUMA, CONTROL GROUP

| INCIDENT | NO. OF PATIENTS |
|---|-----------------|
| One spontaneous abortion | 3 |
| Two spontaneous abortions | 1 |
| One induction of labor | 11 |
| Two cesarean sections | 1 |
| Three cesarean sections | 1 |
| Induction of labor and spontaneous abortion | 2 |
| Difficult forceps delivery and five cesarean sections | 1 |
| Two inductions of labor | 2 |
| One cesarean section and one abortion with dilatation and curettage | 1 |
| Two abortions with dilatation and curettage | 1 |
| One breech delivery | 1 |
| Difficult forceps delivery with cervical laceration | 1 |
| One abortion with dilatation and curettage | 3 |
| Total | 29 |

There were 45 separate "traumatic" episodes which happened to these 29 Rh-negative mothers (Table III).

TABLE III. OBSTETRIC TRAUMA, ISOIMMUNIZED GROUP

| INCIDENT | FREQUENCY OF OCCURRENCE |
|---|-------------------------|
| Spontaneous abortion | 7 |
| Induction of labor | 17 |
| Cesarean section | 11 |
| Incomplete abortion with dilatation and curettage | 6 |
| Difficult forceps delivery | 2 |
| Breech delivery | 1 |
| Cervical laceration | 1 |
| Total | 45 |

Rh Antibody Titers

Most observers follow these Rh-negative pregnancies by antititer determinations. We have found that such data are of little value in forecasting the outcome of any particular pregnancy or of future childbearing. In the series of 24 isoimmunized women, there were 5 with no antepartum titer deter-

mination. These women's serum titers were checked on several occasions by the same laboratory. One woman had no titer to within one week prior to the delivery of a stillborn erythroblastotic fetus. Another without isoimmunization during pregnancy delivered a baby that succumbed to kernicterus on the seventh day, and the mother was then found to have a titer of 1:512 on the tenth postpartum day. This variance in serum titer has been observed by others.^{9, 11}

Comment

Levine¹¹ states that isoimmunization against the Rh factor depends on: (1) combinations of an Rh-negative mother and a fetus whose red blood cells contain the Rh factors, and (2) the inherent genetic capacity to respond to the antigenic stimulus. The whole concept of immunization is exposure to an antigenic stimulus over a long period of time or exposure on several occasions. It is then easy to realize how a pregnancy fulfills these criteria for antigen-antibody reactions. Throughout pregnancy there is an antigen present every day from three weeks on.¹⁵ This antigen of fetal red blood cells, however, is not thought to cross the placental barrier before the fourth or fifth month of pregnancy.¹² Weiner²⁰ states that there is a placental transfer in one of three normal pregnancies.* This fact we have not been able to substantiate, but very recently Mengert and co-workers¹⁴ have shown an interchange of cells from the mother to the fetus, and, therefore, assume an interchange in the reverse direction.

Accumulated evidence by many different observers points to the probability of transfer of fetal red blood cells through the placenta. Of these, Reynolds¹⁸ observation of a pressure gradient between fetal and maternal placental circulation of 30-40 to 10 mm. of mercury might be mentioned. This indicates that blood could travel from the fetus to the mother. The rupture of a thin-walled villus is easily imagined when one considers that the surface of the placenta is from 70 to 120 square feet.¹³ Levine¹⁰ states that only 0.067 c.c. of Rh-positive fetal blood is necessary to immunize an Rh-negative mother. With these points in mind, it may then be assumed that the transfer of fetal cells to the mother could be easily accomplished.²³

Conclusions

In both the study and control groups, the results were evaluated with and without spontaneous abortion (Table IV). We do not find that abortion, either spontaneous or completed by dilatation and curettage, seems to isoimmunize an Rh-negative mother. This is contrary to the thinking of some other investigators.^{4, 16} Dilatation and curettage for incomplete abortions are nearly always performed because of hemorrhage and, therefore, there is not much likelihood of fetal blood passing through to the mother since the hemorrhage would carry it outward.¹²

Induction of labor by medical means or by amniotomy has been mentioned as a traumatic factor producing isoimmunization of Rh-negative women.^{4, 16}

*Since this paper was written, Chown²³ has conclusively proved passage of fetal blood into the maternal circulation.

The figures here recorded do not indicate this to be true. There were 15 patients (23 per cent) in the control group and none in the study group who had induction of labor.

Obstetric procedures play little part in the Rh isoimmunization of any particular woman. Rather, the underlying cause is in accordance with the concepts of Levine,⁹ as previously mentioned.

TABLE IV. OBSTETRIC TRAUMA, SPONTANEOUS ABORTION EXCLUDED

| | STUDY | | CONTROL | |
|---|-------|----|---------|----|
| | NO. | % | NO. | % |
| 1. Patients included | 24 | | 66 | |
| 2. Patients with obstetric incidents other than simple delivery | 4 | 17 | 29 | 44 |
| 3. Patients with obstetric procedures other than spontaneous abortion | 1 | 4 | 25 | 40 |

Summary

1. Sixty-six Rh-negative mothers with homozygous Rh-positive husbands or two or more Rh-positive children have been studied in relation to the incidence of obstetric procedures. None of these women had been immunized. Twenty-nine, or 44 per cent, had a history of obstetric incidents other than routine delivery.

2. Twenty-four Rh-negative immunized mothers were likewise studied in relation to the incidence of obstetric procedures. All but one of these mothers had given birth to an erythroblastotic infant. Seventeen per cent of these patients had experienced obstetric procedures other than routine delivery.

3. Rh antiserum titers were found to be misleading in prognosticating the outcome of the present or future pregnancies.

4. Isoimmunization occurs during normal pregnancy in some women and obstetric factors do not seem to influence this process.

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Discussion

DR. KENNETH S. NICOLAY, Kansas City, Mo.—It is comforting to note that at least Dr. Ehrenberg read our paper which was published last year. He may have missed the point we tried to make, however, of the iatrogenic nature of a high percentage of these Rh tragedies. We did not state that trauma was necessary to produce Rh isoimmunization; only that it seemed to play a part in a sizable percentage of cases. I will agree that blood transfusions should not be considered an obstetrical factor though our "ubiquitously established" blood banks still make mistakes and give Rh-positive blood to Rh-negative individuals, at least in Kansas City.

The small series of 24 patients presented here, and our own series of 73 patients are certainly not statistically significant. It is this fact which probably accounts for the wide variation in results between Dr. Ehrenberg's series and ours.

After reviewing our immunized patients, I have come to the conclusion that Dr. Ehrenberg has not made his point in view of our own findings. I do not understand too clearly whether his 24 immunized patients were his total out of 763 Rh-negative mothers, or whether they were a selected group. For more accurate comparison, from our original 73 patients, I have discarded all who have not been delivered since immunization was discovered, all who were transfused, all with incomplete histories or laboratory studies.

In the selected group of 45 patients, the following factors were found: 21 with completely negative or normal histories; 24 with "obstetrical factors"; 4 traumatic deliveries; 5 manual removal of placentas; 3 induced labors; 3 cesarean sections (all unnecessary); 2 induced abortions; 2 traumatic third stages; 2 combined factors; 1 incomplete abortion with curettage; and 2 spontaneous abortions.

Breech deliveries, forceps deliveries, and other abnormal obstetrical situations that would have no effect on the placental barrier were not included. Even so, 53.4 per cent had "obstetrical" factors in their history and 46.6 per cent did not. Not including spontaneous abortion, 49 per cent and 51 per cent, respectively, were noted.

Dr. Ehrenberg's control series, again, leaves me somewhat confused as to origin. To eliminate confusion, I selected all of our Rh-negative multiparas, with known homozygous husbands, discarding those with heterozygous husbands in spite of the Rh factor of the infants. Of these patients there are 62.

Fifty-three, or 85 per cent, had none of the factors mentioned in the study group. Nine, or 15 per cent, had "obstetrical" factors. These were: 5 spontaneous abortions, 2 followed by curettage; 1 incomplete abortion treated with curettage; 1 cesarean section; 1 manual removal of the placenta; 1 marginal placenta previa with hemorrhage.

Removing the 3 spontaneous abortions, the figures become 90 per cent with no obstetrical factors and 10 per cent with factors. This compares with 46 per cent with no factors and 54 per cent with factors in the immunized patient.

All of our patients were private patients, most of the laboratory work was done in our own office, and all patients were delivered and cared for by either my associate or myself.

I am at a loss to explain the wide difference in results, other than on the basis of the small number of patients involved.

DR. EHRENBERG (Closing).—Answering Dr. Nicolay, our 24 immunized patients were the total number from among the 763 Rh-negative women after the criteria we imposed had been met; likewise the 66 cases in the control group.

A word as to the incidence of hemolytic disease might be of interest. It is estimated that erythroblastosis from Rh sensitization occurs about once in 26 children born to incompatible Rh matings, and about once in 200 deliveries. The actual incidence of the disease, however, is slightly higher, as other antigens such as HBO, Kell, MNS, Kidd, Duffy, etc., have been reported to be causative. A study of neonatal deaths in Hennepin County, Minnesota, has been in progress for some years. During 1952 there were 19,910 live births reported, 99.7 per cent of which occurred in hospitals. Death from hemolytic disease during the neonatal period was reported in 5 of 258 premature infants and 13 of 95 full-term babies. This would mean that hemolytic disease is fatal in about one fifth of the infants born alive as about 100 cases of erythroblastosis should have occurred in the 19,910 deliveries. In addition there were 14 of 287 stillbirths attributed to erythroblastosis. The disease then is not common and the collection of a sufficient number of cases to be statistically significant offers some difficulty.

Our series of cases admittedly is small and one questions the validity of presenting them statistically. Our results were such, however, that we feel that immunization is not due to obvious causes such as obstetrical trauma but rather is due to some unknown factor or factors which await future clarification.

FACTORS AFFECTING PREMATURE NEONATAL MORTALITY*

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SINCE maternal mortality has been approaching the irreducible minimum, more attention of late has been given to the salvaging of infants, particularly the prematures.

With this thought in mind, we undertook the problem of finding the incidence of prematurity as well as the neonatal premature mortality rate at the Indiana University Medical Center (William H. Coleman Hospital) over the five-year period from July 1, 1947, through June 30, 1952. A study of the various factors that might influence the mortality rate of liveborn prematures was made during this same period, the series consisting of six hundred white infants.

In this study a liveborn premature was defined as any infant born alive that weighed between 400 and 2,500 grams, inclusive; while a neonatal premature death was defined as the death of any liveborn premature of the same weight during the first thirty days of life.

These infants were divided into four groups according to their weight, and also as to the two services, private and clinic, as shown in Table I.

On the private service during this period, there were 6,249 liveborn infants, including 74 sets of twins, 64 of whom were premature, with a total of 354 liveborn prematures, an incidence of 5.6 per cent.

On the clinic service, there were 3,500 liveborn infants, including 34 sets of twins, 27 of whom were premature, with a total of 246 liveborn prematures, an incidence of 7.0 per cent.

On the private service, approximately 98 per cent of the cases were handled by Board or Board-qualified men, while the clinic cases were handled by the Chief of Staff, his Assistant, and the House Staff (residents and interns).

In Table I in each weight group of each service are listed: (1) the number of surviving and nonsurviving prematures; (2) the uncorrected mortality rates of each weight group; and (3) the percentage of prematures comprising each weight group.

TABLE I. RELATION OF BIRTH WEIGHT TO MORTALITY

| | WEIGHT IN GRAMS | | | | | | | | TOTAL | |
|--|-----------------|----|-------------|----|-------------|---|-------------|----|-------|----|
| | 400-999 | | 1,000-1,499 | | 1,500-1,999 | | 2,000-2,500 | | | |
| | L | D | L | D | L | D | L | D | L | D |
| <i>Private.</i> — | 0 | 17 | 14 | 14 | 62 | 9 | 226 | 12 | 302 | 52 |
| True mortality | 100 | | 50 | | 12.67 | | 5.04 | | 14.68 | |
| Percentage of total pre-mature infants | 4.8 | | 7.9 | | 20.0 | | 67.2 | | 99.9 | |
| <i>Clinic.</i> — | 2 | 16 | 8 | 15 | 44 | 8 | 143 | 10 | 197 | 49 |
| True mortality | 88.88 | | 65.21 | | 15.38 | | 6.53 | | 19.91 | |
| Percentage of total pre-mature infants | 7.3 | | 9.3 | | 21.1 | | 62.1 | | 99.8 | |

*Presented at the Twenty-third Annual Meeting of the Central Association of Obstetricians and Gynecologists, Columbus, Ohio, Oct. 6, 7, and 8, 1955.

On the private service, there were 354 liveborn prematures with 52 neonatal deaths which makes the uncorrected neonatal premature mortality rate 14.68 per cent. On the clinic service, there were 246 liveborn prematures 49 of whom succumbed, making the uncorrected neonatal premature mortality rate 19.91 per cent.

These mortality rates and the percentage of prematures comprising each weight group closely approximate those reported by Bundesen and associates¹ for Chicago, 1950.

On the private service, though, the number of cases of this study is considerably smaller, the mortality rates of each weight group and the percentage of prematures comprising each weight group compared very favorably with the statistics of Chicago Lying-in Hospital as reported by Potter² in a study covering the same years as this study.

In further tables, we wish to show the influence of other factors on mortality. According to Breese,³ "the effect of other factors influencing mortality is likely to be obscured unless we have some method of correcting mortality figures so that the influence of weight can be eliminated from the comparisons." We have attempted to eliminate this weight factor by the method described by Breese, as follows: "Using the mortality in each weight class of the entire group as the base line, we obtained the expected mortality for each factor as follows: The number of cases in each weight class is multiplied by the mortality for that weight group; the sum of all these is then divided by the total number of cases studied. This will give the expected mortality percentage."

It is then the deviation of the true and expected mortality rates for each individual factor which express its inherent hazard or safety as the true mortality exceeds or falls below the expected mortality, rather than the simple true mortality figure itself. To emphasize this, to each of the following tables has been added a column labeled "Deviation" (Dev.), with an appropriate plus (+) or minus (-) indication of such divergence. For example, in Table II, showing the effect of parity on mortality, the actual calculation of the expected mortality of primiparas on the private service is as follows:

100

×

7

=

700

50

×

11

=

550

12.67

×

32

=

405.44

5.04

×

112

=

564.48

162

2219.92

2219.92

162

=

13% expected mortality

TABLE II. EFFECT OF PARITY ON MORTALITY

| | WEIGHT IN GRAMS | | | | | | | | TOTAL | | | PERCENTAGE | | |
|-----------------------|-----------------|----|-------------|---|-------------|---|-------------|---|---------------------------|----|-----|------------|------|------|
| | 400-999 | | 1,000-1,499 | | 1,500-1,999 | | 2,000-2,500 | | | | | | | |
| | L | D | L | D | L | D | L | D | L | D | T | TRUE | EXP. | DEV. |
| <i>Private.—</i> | | | | | | | | | | | | | | |
| Primiparas | 0 | 7 | 4 | 7 | 29 | 3 | 108 | 4 | 141 | 21 | 162 | 12.9 | 13.7 | -1 |
| Multiparas | 0 | 10 | 10 | 7 | 33 | 6 | 118 | 8 | 161 | 31 | 192 | 16.1 | 15.5 | +1 |
| <i>Clinic.—</i> | | | | | | | | | | | | | | |
| Primiparas | 0 | 6 | 0 | 7 | 17 | 3 | 47 | 5 | 64 | 21 | 85 | 24.7 | 19.2 | +6 |
| Multiparas | 2 | 10 | 8 | 8 | 27 | 5 | 96 | 5 | 133 | 28 | 161 | 17.3 | 20.2 | -3 |
| <i>True Mortality</i> | | | | | | | | | <i>Expected Mortality</i> | | | | | |
| = | | | | | | | | | 100 × 7 = 700 | | | | | |
| | | | | | | | | | 50 × 11 = 550 | | | | | |
| | | | | | | | | | 12.67 × 32 = 405.44 | | | | | |
| | | | | | | | | | 5.04 × 112 = 564.48 | | | | | |
| | | | | | | | | | 2219.92 | | | | | |
| | | | | | | | | | 162 | | | | | |
| | | | | | | | | | = 13.7% | | | | | |

An actual or true mortality rate below the expected mortality would represent an improved fetal salvage whereas a true mortality rate greater than the expected would represent an abnormal fetal loss.

In this group, the primiparas of the private service, the true mortality was 12.9 per cent, a deviation of minus one. Therefore, one might conclude that primiparity had no effect on the mortality of prematures of this service. Practically the same conclusions can be drawn with the multiparas of the private service and of both the parity groups of the clinic service.

It is interesting to note that on the private service the cases are about equally divided between primiparas and multiparas; but on the clinic service there were about twice as many prematures among the multiparas as among the primiparas.

In Table III, the effect of gestation on mortality is recorded.

TABLE III. EFFECT OF LENGTH OF GESTATION ON MORTALITY

| WEEKS' GESTATION | WEIGHT IN GRAMS | | | | | | | | TOTAL | | | PERCENTAGE | | |
|------------------|-----------------|----|-------------|---|-------------|---|-------------|---|-------|----|-----|------------|------|------|
| | 400-900 | | 1,000-1,499 | | 1,500-1,999 | | 2,000-2,500 | | | | | | | |
| | L | D | L | D | L | D | L | D | L | D | T | TRUE | EXP. | DEV. |
| <i>Private.—</i> | | | | | | | | | | | | | | |
| Over 40 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 1 | 4 | 1 | 5 | 20 | 5 | +15 |
| 38 to 40 | 0 | 0 | 2 | 2 | 9 | 3 | 95 | 4 | 106 | 9 | 115 | 7.8 | 7.4 | 0 |
| 34 to 37 | 0 | 0 | 5 | 2 | 30 | 4 | 113 | 1 | 148 | 7 | 155 | 4.5 | 8.7 | - 4 |
| 30 to 33 | 0 | 1 | 4 | 7 | 22 | 2 | 9 | 5 | 35 | 15 | 50 | 30 | 19.4 | +10 |
| Under 30 | 0 | 16 | 2 | 2 | 0 | 0 | 0 | 0 | 2 | 18 | 20 | 90.0 | 90.0 | 0 |
| Not stated | 0 | 0 | 1 | 1 | 1 | 0 | 5 | 1 | 7 | 2 | 9 | | | |
| <i>Clinic.—</i> | | | | | | | | | | | | | | |
| Over 40 | 0 | 0 | 0 | 0 | 3 | 0 | 6 | 0 | 9 | 0 | 9 | 0.0 | 9.4 | -9 |
| 38 to 40 | 0 | 0 | 0 | 2 | 7 | 1 | 48 | 6 | 55 | 9 | 64 | 14 | 9.4 | +5 |
| 34 to 37 | 0 | 0 | 1 | 2 | 22 | 4 | 73 | 2 | 96 | 8 | 104 | 7.6 | 10.4 | -3 |
| 30 to 33 | 0 | 3 | 5 | 7 | 10 | 2 | 10 | 1 | 25 | 13 | 38 | 34.2 | 34.3 | 0 |
| Under 30 | 2 | 13 | 2 | 3 | 2 | 0 | 1 | 0 | 7 | 16 | 23 | 69.5 | 73.7 | -4 |
| Not stated | 0 | 0 | 0 | 1 | 0 | 1 | 5 | 1 | 5 | 3 | 8 | | | |

The period of gestation in this study was based on the patient's history of the first day of her last menstrual period. In the private group, it is seen that all the infants under 30 weeks' gestation weighed less than 1,500 grams, while 96.9 of the premature infants that were of 34 weeks' gestation or more weighed over 1,500 grams. It is noted that 5 of the prematures were of 41 weeks' gestation or more.

In the clinic group, 87 per cent of the prematures under 30 weeks' gestation weighed less than 1,500 grams, while 97.9 per cent of the prematures that were of 34 weeks' gestation or more weighed more than 1,500 grams. It is also interesting to note here that 9 (3.7 per cent) were of 41 weeks' gestation or more.

Whether or not any conclusions can be reached from these two tables regarding the effect of gestation on mortality may be questionable, because the number of cases in each section is small; therefore, there may be a sampling error.

In Table IV is recorded the effect of sex on mortality. It can be seen in both services that sex has no effect on mortality.

According to Eastman,⁴ term male births exceed female in the ratio of 106 to 100.

A similar ratio is found in this study when both the private and clinic services are combined. When they are separated, however, in the private section the males outnumber the females 108 to 100, while in the clinic section it is 103 to 100.

In the private section, the true mortality of both the males and the females is the same, while in the clinic group the mortality of the males is 7 per cent higher.

TABLE IV. EFFECT OF SEX ON MORTALITY

| | WEIGHT IN GRAMS | | | | | | | | TOTAL | | | MORTALITY PERCENTAGE | | |
|-------------------|-----------------|----|-------------|----|-------------|---|-------------|----|-------|----|-----|----------------------|------|------|
| | 400-999 | | 1,000-1,499 | | 1,500-1,999 | | 2,000-2,500 | | | | | TRUE | EXP. | DEV. |
| | L | D | L | D | L | D | L | D | L | D | T | | | |
| <i>Private.</i> — | | | | | | | | | | | | | | |
| Males | 0 | 7 | 5 | 9 | 28 | 6 | 122 | 5 | 155 | 27 | 182 | 14.8 | 13.5 | +1 |
| Females | 0 | 10 | 9 | 5 | 34 | 3 | 100 | 7 | 143 | 25 | 168 | 14.8 | 16.1 | -1 |
| Not stated | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 4 | 0 | 4 | 0.0 | 5.0 | -5 |
| Total | 0 | 17 | 14 | 14 | 62 | 9 | 226 | 12 | 302 | 52 | 354 | | | |
| <i>Clinic.</i> — | | | | | | | | | | | | | | |
| Males | 2 | 10 | 4 | 11 | 22 | 2 | 68 | 5 | 96 | 28 | 124 | 22.5 | 23.3 | -1 |
| Females | 0 | 16 | 4 | 3 | 22 | 6 | 75 | 4 | 101 | 19 | 120 | 15.8 | 16.1 | 0 |
| Not stated | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 2 | 2 | 100.0 | 35.8 | +64 |
| Total | 2 | 26 | 8 | 15 | 44 | 8 | 143 | 10 | 197 | 49 | 246 | | | |

TABLE V. EFFECT OF LENGTH OF LABOR ON MORTALITY

| HOURS | WEIGHT IN GRAMS | | | | | | | | TOTAL | | | PERCENTAGE | | |
|-------------------|-----------------|----|-------------|---|-------------|---|-------------|---|-------|----|-----|------------|------|------|
| | 400-999 | | 1,000-1,499 | | 1,500-1,999 | | 2,000-2,500 | | | | | | | |
| | L | D | L | D | L | D | L | D | L | D | T | TRUE | EXP. | DEV. |
| <i>Private.</i> — | | | | | | | | | | | | | | |
| None | 0 | 0 | 2 | 2 | 6 | 1 | 16 | 0 | 24 | 3 | 27 | 11.1 | 13.6 | -3 |
| 0 to 10 | 0 | 12 | 8 | 6 | 31 | 6 | 119 | 8 | 158 | 32 | 190 | 16.8 | 15.8 | +1 |
| 11 to 20 | 0 | 2 | 4 | 3 | 15 | 1 | 61 | 2 | 80 | 8 | 88 | 9.0 | 12.1 | -3 |
| 21 to 30 | 0 | 0 | 0 | 1 | 6 | 0 | 8 | 0 | 14 | 1 | 15 | 6.6 | 11.0 | -4 |
| 31 plus | 0 | 0 | 0 | 2 | 0 | 1 | 6 | 2 | 6 | 5 | 11 | 45.4 | 13.9 | +32 |
| Not stated | 0 | 3 | 0 | 0 | 4 | 0 | 16 | 0 | 20 | 3 | 23 | | | |
| <i>Clinic.</i> — | | | | | | | | | | | | | | |
| None | 0 | 0 | 2 | 0 | 4 | 1 | 3 | 0 | 9 | 1 | 10 | 10.0 | 22.6 | -13 |
| 0 to 10 | 2 | 12 | 4 | 7 | 21 | 2 | 94 | 5 | 121 | 26 | 147 | 17.6 | 20.0 | -3 |
| 11 to 20 | 0 | 1 | 1 | 5 | 12 | 2 | 26 | 2 | 39 | 10 | 49 | 20.4 | 17.9 | +3 |
| 21 to 30 | 0 | 0 | 0 | 1 | 3 | 0 | 8 | 0 | 11 | 1 | 12 | 8.3 | 13.6 | -5 |
| 31 plus | 0 | 0 | 0 | 0 | 1 | 1 | 3 | 1 | 4 | 2 | 6 | 33.3 | 9.1 | +24 |
| Not stated | 0 | 3 | 1 | 2 | 3 | 2 | 9 | 2 | 13 | 9 | 22 | | | |

Table V records the effect of the length of labor on the mortality rate of the prematures. There is very little variation between the true and expected mortality rates in the various groupings in each section except in the grouping "31 hours plus." Even though the number of cases is small, the deviation between the true and expected mortality rates in both services is great. Therefore, one might surmise it is not wise to let mothers of premature infants labor too long. Particularly is this so since in the "no labor" category, all abdominal deliveries, there was no deleterious effect on the premature.

Table VI shows the effect of the type of delivery on the mortality of the prematures of the two services.

On the private service, there is no great variation between the two types of mortality except in the two following groups: the low forceps without episiotomy, and the internal podalic version and extraction. The number of cases in both of these groups is so small, however, that it cannot be considered statistically significant.

On the clinic service, the only group that had a true mortality considerably higher than the expected mortality was that delivered by breech extraction with episiotomy. This might possibly be explained on the basis of the relative inexperience of the house staff in breech deliveries.

On the private service, the greatest number of deliveries (43.2 per cent) were accomplished by low forceps and episiotomy; while on the clinic service the greatest number of deliveries (29.2 per cent) were accomplished by a spontaneous delivery without an episiotomy.

The incidence of cesarean section was 9.8 per cent on the private service which was twice as great as that on the clinic service, 4.8 per cent.

When the spontaneous deliveries with episiotomy and without episiotomy on the private service are compared, the true mortality of the latter groups is 4.5 times as great even though the expected mortality is only 2.5 times as great.

Also, on the private service with the use of low forceps the true mortality was over three times as great in the group without episiotomy as compared with the group that used episiotomy even though the expected mortality for both groups was essentially the same.

TABLE VI. EFFECT OF TYPE OF DELIVERY ON MORTALITY

| TYPE OF DELIVERY | WEIGHT IN GRAMS | | | | | | | | TOTAL | | | MORTALITY PERCENTAGE | | | DEL. % |
|--------------------------------------|-----------------|----|-----------------|----|-----------------|---|-----------------|----|-------|----|-----|-------------------------|------|------|-----------|
| | 400- 999 | | 1,000- 1,499 | | 1,500- 1,999 | | 2,000- 2,500 | | | | | | | | |
| | L | D | L | D | L | D | L | D | L | D | T | TRUE | EXP. | DEV. | |
| <i>Private.—</i> | | | | | | | | | | | | | | | |
| Cesarean section | 0 | 0 | 2 | 2 | 8 | 1 | 22 | 0 | 32 | 3 | 35 | 8.5 | 12.1 | —4 | 9.8 |
| Spontaneous with episiotomy | 0 | 1 | 5 | 0 | 13 | 2 | 32 | 2 | 50 | 5 | 55 | 9.0 | 12.9 | —4 | 15.5 |
| Spontaneous with- out episiotomy | 0 | 9 | 3 | 2 | 5 | 1 | 14 | 4 | 22 | 16 | 38 | 42.1 | 34.6 | +8 | 10.7 |
| Low forceps with episiotomy | 0 | 1 | 2 | 4 | 23 | 3 | 117 | 3 | 142 | 11 | 153 | 7.1 | 8.7 | —2 | 43.2 |
| Low forceps with- out episiotomy | 0 | 0 | 0 | 0 | 1 | 0 | 2 | 1 | 3 | 1 | 4 | 25.0 | 6.9 | +18 | 1.1 |
| Midforceps and episiotomy | 0 | 0 | 0 | 0 | 1 | 0 | 8 | 0 | 9 | 0 | 9 | 0.0 | 5.8 | —6 | 2.8 |
| Spontaneous breech | 0 | 4 | 2 | 3 | 5 | 0 | 2 | 0 | 9 | 7 | 16 | 43.7 | 45.2 | —2 | 4.5 |
| Breech extraction with episiotomy | 0 | 1 | 0 | 3 | 5 | 2 | 25 | 1 | 30 | 7 | 37 | 18.9 | 12.6 | +6 | 10.4 |
| Internal podalic version | 0 | 1 | 0 | 0 | 1 | 0 | 2 | 1 | 3 | 2 | 5 | 40.0 | 25.5 | +15 | 1.4 |
| Not stated | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 2 | 0 | 2 | 0.0 | 5.0 | —5 | .5 |
| Total | 0 | 17 | 14 | 14 | 62 | 9 | 226 | 12 | 302 | 52 | 354 | | | | 99.9 |
| <i>Clinic.—</i> | | | | | | | | | | | | | | | |
| Cesarean section | 0 | 0 | 2 | 0 | 4 | 1 | 5 | 0 | 11 | 1 | 12 | 8.3 | 19.9 | —12 | 4.8 |
| Spontaneous with episiotomy | 1 | 0 | 0 | 1 | 10 | 0 | 24 | 2 | 35 | 3 | 38 | 7.8 | 12.5 | —5 | 15.4 |
| Spontaneous with- out episiotomy | 1 | 5 | 1 | 4 | 15 | 4 | 39 | 3 | 56 | 16 | 72 | 22.2 | 19.8 | +2 | 29.2 |
| Low forceps with episiotomy | 0 | 0 | 0 | 4 | 6 | 0 | 43 | 2 | 49 | 6 | 55 | 10.9 | 11.7 | —1 | 22.3 |
| Low forceps with- out episiotomy | 0 | 1 | 0 | 0 | 1 | 0 | 8 | 0 | 9 | 1 | 10 | 10.0 | 15.6 | —6 | 4.0 |
| Midforceps with episiotomy | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 2 | 0 | 2 | 0.0 | 35.8 | —36 | .8 |
| Spontaneous breech | 0 | 7 | 3 | 1 | 1 | 0 | 4 | 2 | 8 | 10 | 18 | 55.5 | 52.0 | +4 | 7.3 |
| Breech extraction with episiotomy | 0 | 2 | 1 | 5 | 7 | 3 | 15 | 1 | 23 | 11 | 34 | 32.3 | 20.6 | +12 | 13.8 |
| Internal podalic version | 0 | 1 | 0 | 0 | 0 | 0 | 3 | 0 | 3 | 1 | 4 | 25.0 | 27.1 | —2 | 1.6 |
| Not stated | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0.0 | 6.5 | —7 | .4 |
| Total | 2 | 16 | 8 | 15 | 44 | 8 | 143 | 10 | 197 | 49 | 246 | | | | 99.6 |

Practically the same findings are noted on the clinic service, but they are not quite as dramatic.

Nevertheless, it appears that these statistics bear out the old aphorism, "The greater the prematurity, the more generous the episiotomy."

The total rate of breech deliveries of premature infants on the private service was 16.3 per cent, and that on the clinic service, 22.7 per cent.

By the spontaneous breech delivery is meant the delivery of an infant without an episiotomy and with or without manual aid. In the group of breech extraction with episiotomy manual aid was employed.

Another interesting observation is noted on studying Table VI. On the private service, when the "spontaneous delivery with episiotomy" and "breech extraction with episiotomy" groups are compared it is observed that the expected mortality of both groups is the same, yet the true mortality of the breech delivery group is twice as great.

On the clinic service, by the same comparison, even though the expected mortality rate of the "breech" group is 1.5 times as great as that of the "spontaneous" group, yet the true mortality of the former group is four times as great.

These findings tend to concur with those of other authors,^{3, 5, 6} that breech delivery is more dangerous for prematures than most other forms of vaginal delivery.

The authors also wonder if these observations are not a strong point in favor of external version, particularly when one keeps in mind that 98 per cent of the private deliveries were done by Board or Board-qualified men.

Also in a study of this table, it is observed that there were 11 midforceps deliveries with episiotomy (9 on the private service) with no fetal mortality.

Table VII records the effect of sedation and anesthesia on mortality of the prematures of both services.

TABLE VII. EFFECT OF SEDATION AND ANESTHESIA ON MORTALITY

| SEDATION AND/OR ANESTHESIA | WEIGHT IN GRAMS | | | | | | | | TOTAL | | | MORTALITY PERCENTAGE | | |
|-------------------------------|-----------------|----|-------------|----|-------------|---|-------------|----|-------|----|-----|-------------------------|------|------|
| | 400-999 | | 1,000-1,499 | | 1,500-1,999 | | 2,000-2,500 | | | | | | | |
| | L | D | L | D | L | D | L | D | L | D | T | TRUE | EXP. | DEV. |
| <i>Private.</i> — | | | | | | | | | | | | | | |
| None | 0 | 3 | 1 | 2 | 3 | 0 | 0 | 0 | 4 | 5 | 9 | 55.5 | 54.2 | +1 |
| Sedation | 0 | 5 | 1 | 2 | 2 | 0 | 4 | 2 | 7 | 9 | 16 | 56.2 | 44.0 | +12 |
| Conduction | 0 | 4 | 2 | 1 | 10 | 1 | 27 | 1 | 39 | 7 | 46 | 15.2 | 18.0 | -3 |
| Inhalation | 0 | 1 | 2 | 2 | 9 | 1 | 32 | 4 | 43 | 8 | 51 | 15.6 | 14.1 | +2 |
| Sedation and inhalation | 0 | 3 | 5 | 4 | 25 | 4 | 127 | 4 | 157 | 15 | 172 | 8.7 | 9.9 | -1 |
| Sedation and conduction | 0 | 1 | 3 | 3 | 13 | 3 | 36 | 1 | 52 | 8 | 60 | 13.3 | 21.4 | -8 |
| Not stated | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 | 0.0 | |
| Total | 0 | 17 | 14 | 14 | 62 | 9 | 226 | 12 | 302 | 52 | 354 | | | |
| <i>Clinic.</i> — | | | | | | | | | | | | | | |
| None | 0 | 3 | 2 | 1 | 9 | 1 | 10 | 1 | 21 | 6 | 27 | 22.2 | 25.4 | -3 |
| Sedation | 0 | 6 | 0 | 2 | 0 | 1 | 9 | 0 | 9 | 9 | 18 | 50.0 | 40.9 | +9 |
| Conduction | 0 | 2 | 1 | 1 | 5 | 3 | 17 | 0 | 23 | 6 | 29 | 20.6 | 18.6 | +2 |
| Inhalation | 0 | 5 | 1 | 5 | 10 | 2 | 31 | 5 | 42 | 17 | 59 | 28.8 | 21.2 | +8 |
| Sedation and inhalation | 1 | 0 | 2 | 5 | 15 | 1 | 53 | 4 | 71 | 10 | 81 | 12.3 | 14.3 | -2 |
| Sedation and conduction | 1 | 0 | 2 | 1 | 5 | 0 | 23 | 0 | 31 | 1 | 32 | 3.1 | 15.9 | -13 |
| Not stated | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 | 0.0 | |
| Total | 2 | 16 | 8 | 15 | 44 | 8 | 143 | 10 | 197 | 49 | 246 | | | |

In this table, "sedation" means that these mothers received some type of analgesic drug or combination thereof (barbiturates, Demerol, scopolamine, or rectal ether); while "inhalation" means that they received nitrous oxide, cyclopropane, ether, or any combination thereof as an anesthetic. Conduction anesthesia was given in the form of a "low" spinal (saddle block), local, or pudendal block.

On the private service 94 per cent of the conduction anesthetics were spinal, while on the clinic service there were 89 per cent spinal.

Although the separate dosage listings of the various analgesic drugs were not made, many of these mothers of premature infants had smaller dosages than are commonly used in term labors.

On the private service 70 per cent of the patients received some type of analgesia, as compared with 53 per cent of the clinic patients.

On both services, the most common procedure was to use some analgesic drug with an inhalation anesthetic. This was employed in 48 per cent of the private cases, and 32 per cent of the clinic cases.

On neither service was there any great divergence between the true and the expected mortality rates except perhaps on the private service. Here, it seemed that only those cases in which sedation was used fared the worst.

One might suppose, at first thought, that those cases in which a conduction anesthetic only was used would do best. This table does not bear this out, however. We conclude from it that some form of analgesia combined with a conduction anesthetic will have a beneficial effect on the premature mortality rate as evidenced by a divergence of minus 8 on the private service and minus 13 on the clinic service.

West and associates⁶ also found that conduction anesthesia alone did not give the best results.

Table VIII records the effect of maternal complications on premature mortality.

TABLE VIII. EFFECT OF MATERNAL COMPLICATIONS ON PREMATURE MORTALITY

| COMPLICATION | WEIGHT IN GRAMS | | | | | | | | TOTAL | | | MORTALITY PERCENTAGE | | | INCIDENCE OF COMPLICATIONS |
|--------------------------------|-----------------|----|-------------|-----|-------------|---|-------------|-----|-------|-----|------|----------------------|------|------|----------------------------|
| | 400-999 | | 1,000-1,499 | | 1,500-1,999 | | 2,000-2,500 | | | | | | | | |
| | L | D | L | D | L | D | L | D | L | D | T | TRUE | EXP. | DEV. | |
| Private.— | | | | | | | | | | | | | | | |
| None | 0 | 8 | 5 | 3 | 23 | 4 | 126 | 6 | 154 | 21 | 175 | 12.0 | 12.6 | −1 | 49.4 |
| Toxemia | 0 | 0 | 2 | 2 | 9 | 0 | 17 | 1 | 28 | 3 | 31 | 9.6 | 13.0 | −3 | 8.7 |
| Premature rupture of membranes | 0 | 1 | 5 | 4 | 17.5 | 1 | 54.5 | 0.5 | 77 | 6.5 | 83.5 | 7.7 | 11.9 | −4 | 23.5 |
| Abruptio placentae | 0 | 7 | 2 | 1.5 | 8 | 0 | 12.5 | 1 | 22.5 | 9.5 | 32 | 29.6 | 32.6 | −3 | 9.0 |
| Placenta previa | 0 | 0 | 0 | .5 | 1 | 1 | 4 | 0.5 | 5 | 2 | 7 | 28.5 | 10.4 | +18 | 1.9 |
| Other | 0 | 1 | 0 | 3 | 3.5 | 3 | 12 | 3 | 15.5 | 10 | 25.5 | 39.2 | 15.9 | +23 | 7.0 |
| Total | 0 | 17 | 14 | 14 | 62 | 9 | 226 | 12 | 302 | 52 | 354 | | | | 99.5 |
| Clinic.— | | | | | | | | | | | | | | | |
| None | 0 | 7 | 0 | 6 | 12 | 3 | 62 | 5 | 74 | 21 | 95 | 22.1 | 17.5 | +5 | 38.6 |
| Toxemia | 0 | 0 | 1 | 1 | 8.5 | 0 | 20 | 1 | 29.5 | 2 | 31.5 | 6.3 | 12.6 | −6 | 12.8 |
| Premature rupture of membranes | 0 | 1 | 2 | 1 | 9.8 | 2 | 29 | 3 | 40.8 | 7 | 47.8 | 14.6 | 14.1 | +1 | 19.4 |
| Abruptio placentae | 1 | 4 | 2 | 6 | 8.3 | 2 | 18 | 0 | 29.3 | 12 | 41.3 | 29.0 | 30.0 | −1 | 16.8 |
| Placenta previa | 0 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 3 | 1 | 4 | 25.0 | 44.0 | −19 | 1.6 |
| Other | 1 | 3 | 2 | 1 | 4.3 | 1 | 13 | 1 | 20.3 | 6 | 26.3 | 22.7 | 27.5 | −5 | 10.7 |
| Total | 2 | 16 | 8 | 15 | 44 | 8 | 143 | 10 | 197 | 49 | 246 | | | | 99.9 |

[illegible]

On the private service, the autopsy rate was 78 per cent; on the clinic service, 63 per cent.

On the private service, the most common cause of death was prematurity; this includes atelectasis. When combined with hyaline membrane, 48.7 per cent of the deaths fall into this category. The next most common cause of death is congenital anomalies, which accounts for 21.9 per cent, while birth injury is third and accounts for 12.1 per cent of the deaths.

On the clinic service, the order is prematurity or atelectasis, which, if hyaline membrane is included, accounted for 41.8 per cent, followed by birth injury, 19.3 per cent, and congenital anomalies, 12.9 per cent.

The infections included: (1) pneumonia, 2 cases on the private service and 4 on the clinic service; (2) enterocolitis, one case each on the private and clinic services. Of the infants who lived longer than 72 hours 40 per cent on the private service and 44 per cent on the clinic service died from infectious lesions.

Under the grouping "other," the one death on the private service was attributed to Potter's disease. On the clinic service, one of the 2 deaths was due to Ritter's disease, while the other one was attributed to anesthesia on the surgical service as an esophageal fistula was being corrected.

As to the age at death, 88.3 per cent of the prematures on the private service died within the first seventy-two hours, while on the clinic service only 73.2 per cent died within the first seventy-two hours.

Conclusions

1. From July 1, 1947, through June 30, 1952, at the Indiana University Medical Center (William H. Coleman Hospital) the uncorrected neonatal mortality rate of premature white infants on the private service was 14.68 per cent, with an incidence of 5.6 per cent of liveborn prematures. On the clinic service, the uncorrected neonatal mortality rate of premature white infants was 19.91 per cent, with an incidence of 7.0 per cent of liveborn prematures.

2. Using Breese's formula, thereby eliminating the influence of weight, an attempt was made to show the effects of various factors on premature neonatal mortality rates.

3. Sex, parity, and the length of gestation had no deleterious effect on premature neonatal mortality rates.

4. The length of labor had no ill effects on the survival of premature infants unless it was 31 hours or longer.

5. Episiotomy has a beneficial result on the survival of prematures.

6. Breech delivery with episiotomy is much more hazardous for prematures than spontaneous cephalic delivery with episiotomy. This supports the rationale of external version when dealing with the delivery of premature babies presenting by the breech.

7. Cesarean section has no deleterious effect on the survival of prematures.

8. As far as sedation and anesthesia are concerned, it appears that some type of sedation in conjunction with a conduction anesthetic has the most beneficial effects on maintaining life in the premature.

9. Premature rupture of the membranes, toxemia, and abruptio placentae caused no fetal risk per se.

10. On the private service the chief causes of death were as follows: prematurity, combined with hyaline membrane (48.9 per cent), congenital anomalies (21.9 per cent), and birth injuries (12.1 per cent). On the clinic service the order was: prematurity combined with hyaline membrane (41.8 per cent), birth injuries (19.3 per cent), and congenital anomalies (12.9 per cent).

11. On the private service approximately 88 per cent of the deaths occurred within the first 72 hours of life as compared with 73 per cent on the clinic service.

12. On the private service, 40 per cent of the deaths of premature infants after 72 hours were due to an infectious lesion. This was true of 44 per cent on the clinic service.

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621 HUME MANSUR BUILDING

Discussion

DR. JOHN PARKS, Washington, D. C.—The problems of prematurity are threefold: prevention of the causes; management of the labors; and care of the newborn. The obstetrician's interest if not his practice should go well beyond the birth hour of the premature, for it is in this large group of little people that the end results of an incomplete and often imperfect pregnancy can be witnessed.

Why does approximately one out of fifteen pregnancies terminate with the birth of a premature infant? How may the physician recognize conditions which lead to premature birth early and how may these early births be prevented?

The authors have given several clues to these questions, some of which seem to deserve expansion by discussion. For example, 85 per cent of their twin pregnancies terminated prematurely. This is more than ten times the premature birth rate for single pregnancies. Why? Woman is the only mammal with the potential of producing multiple births who during her waking, walking, working day carries the long axis of her pregnant uterus perpendicular to the earth's surface with the cervix at the lower pole of gravity. Overdistention and posture produce premature twin birth. How may this be prevented? Early diagnosis by abdominal, vaginal, and x-ray examination permits time for treatment. Depending upon the degree of cervical effacement and dilatation as determined by vaginal examination, partial to complete bed rest in the last weeks of pregnancy will permit the majority of mothers to carry their twin pregnancies to maturity.

The authors have found, as has been true in other studies, that breech delivery is the least safe manner of delivery in premature birth. The problem of premature breech delivery is usually not pelvic bone or perineal muscle resistance, but rather the wedging of a small fetus in an unprepared lower uterine segment with the largest part, the head, coming last. Contraction of the lower uterine segment about the neck and head can be prevented by the insertion of an extraovular bag when the cervix is 3 to 4 cm. dilated. A large bag causes retraction of the lower segment and dilation of the cervix which permits passage of the fetus without undue pressures. Birth should follow immediately after expulsion of the bag. This is a life-preserving procedure in breech delivery of the premature.

Nontraumatic external version when feasible, carefully considered analgesia in combination with conduction anesthesia, and liberal episiotomy in the conduct of premature delivery are all excellent suggestions.

In the group of 35 infants delivered prematurely by cesarean section was too early election of repeat cesarean section a factor in the birth of any of these infants before maturity? On our Service this is one man-made cause of prematurity which usually can be corrected by consultation.

It is interesting to find in the authors' report that premature rupture of the membranes, toxemia, and abruptio placentae have not influenced the neonatal survival rate of prematures. Fetal deaths have not been included in this study, and the numbers reported in these categories seem too small to justify any broad statement about the influence of early rupture of the membranes, toxemia, and abruptio placentae on the life of the fetus and newborn infant.

In evaluating survival rates Dr. Mather and Dr. McCormick have tended to attribute gains and losses almost entirely to obstetric procedures. Certainly, their pediatric and their nursing staffs must have had an influential part in this program of care of the premature, particularly for those newborn infants who survived the first twenty-four hours after birth.

DR. MCCORMICK (Closing).—We have been advocates of external version for some time, performing it after the thirty-fourth to the thirty-fifth week. I wonder if we should do our versions in the office as soon as we are sure of our diagnosis.

The nurses had a lot to do with the survival of these babies. Approximately 59 per cent of the premature infants of the private service died within the first twelve hours; we have to attribute this to the obstetrician rather than to the pediatrician or the nursing staff.

VAGINAL CYTOLOGY AS AN INDEX OF THE EXPECTED DATE OF CONFINEMENT*

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THE desire of a pregnant patient and of her physician to know the fetal age and the approximate date of expected confinement is a normal and human desire motivated by interest and by social convenience. Under some circumstances, however, the question of the age of the fetus and the reasonably precise calculation of the due date takes on an additional sense of medical urgency. Such obstetric circumstances would include: (a) the selection of the date for an elective repeat cesarean section; (b) the selection of a delivery date for the diabetic pregnant patient whose pregnancy is to be interrupted before term; (c) the selection of a date to which a known obstetric complication must be carried to achieve fetal viability (i.e., placenta previa, etc.); (d) the postmaturity syndrome recently restressed by Stewart Clifford¹ and his co-workers in which the fetus outgrows the aging placenta and loses weight as it gains an increasing chance of antepartum or intrapartum death.

It is not the purpose of this paper to debate or discuss the validity of any of these potential indications but to stress that accuracy in the determination of the due date can become a matter of medical concern. Furthermore, of the group just cited, postmaturity, even if it were not associated with an increased fetal loss, always seems to present an emotional crisis. To quote Stewart²: "When a patient passes the estimated date of confinement, the uncertainty of postmaturity immediately enters the clinical picture. The expectant mother becomes anxious about the size and health of her baby. Family and friends become concerned. The conscientious obstetrician faces additional decisions. He wonders whether the reported date of the last menstruation is accurate. Clinical and x-ray examinations may err in the prediction of the size and maturity of the baby in utero."

Of the currently accepted techniques for determining the stage of a pregnancy, the first group are those that depend upon estimation of the fetal size. Ahlfeld's rule, based on the caliper measurement from cervix to fundus, and MacDonald's rule, based on the measurement from symphysis to fundus, have tradition and experience behind them. The clinical estimation of the fetal weight by abdominal palpation can be surprisingly accurate in experienced hands.

Of the methods in this group it should be noted that they depend fundamentally on a constant rate of fetal growth. Those forms of postmaturity,

*Presented at the Twenty-third Annual Meeting of the Central Association of Obstetricians and Gynecologists, Columbus, Ohio, Oct. 6, 7, and 8, 1955.

however, which represent relative placental insufficiency, are associated with a baby who is losing weight, and in some of the most troublesome of the obstetric problems these techniques for determining term are of lessened value.

Those techniques which rest on history revolve chiefly around the date of occurrence of the last menstrual period and the date that quickening was felt. Stewart's² comparative study of the dates of the last menstrual period and the date of the ovulation of conception indicates the potential fallacy in the history of the last menstrual period. Similarly, a review of records in this clinic has revealed patients who produced a term baby by all physical criteria, yet whose error in due date, calculated on the basis of the last menstrual period, ranged from minus 60 to plus 48 days around the date of delivery. Of quickening it need only be pointed out that it is a concomitant of almost all advanced cases of pseudocyesis and can be subject to greater error than the memory of the date of the last menstrual period.


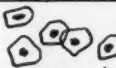
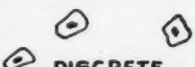
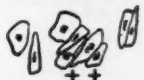
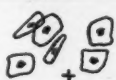
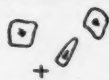






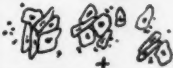
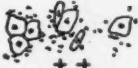

| TYPE | UP TO 39 WEEKS ADVANCED PREGNANCY | 1 TO 6 DAYS PRIOR TO "TERM" | 1 DAY PRIOR TO DELIVERY |
|-----------------|---|---|--|
| DESQUAMATION |  IN PLAQUES |  DENSE ± |  DISCRETE |
| NAVICULAR CELLS |  ++ |  + |  ± |
| CYTOPLASM |  GOOD COLOR |  ± GOOD COLOR |  PALE COLOR |
| CELL VITALITY |  +++ |  ++ |  + |
| LEUCOCYTES |  + |  ++ |  +++ |
| MUCUS | ± | + | ++ |

Fig. 1.

Those methods of ascertaining whether or not the patient is at term that revolve around physical examination of the mother rest principally with the determination of cervical "ripeness." This sign, when positive, is of tremendous assistance, but, unfortunately, in many of the cases of genuine postmaturity, as well as in all cases in which there is an elective early interruption of the pregnancy, it is not present on examination. This sign actually, of course, indicates that the patient is ready to be delivered, not that the baby is ready to be born.

Finally, those techniques which rest on x-ray examination can be grouped under the determinations of the fetal head size and the sequence of appearance

of the epiphyses. The determination of fetal head size is customarily achieved by the method of Ball³ and the resulting figures then related to the standard measurement chart of Scammon and Calkins.⁴ The latter gives standard mean head size measurements which are reliable, but the former will give head size determinations that often are somewhat approximate.⁵ The time sequence of the development of epiphyses in the fetal long bones is reasonably consistent, and when they are adequately visualized the distal femoral and the proximal tibial epiphyses together are reasonably reliable evidences of 37 or 38 weeks of gestation. Even in the term child, however, these can be difficult to visualize after delivery and not infrequently are poorly visualized or unseen when the fetus is within the uterus.⁵

Under the appropriate circumstances any one of these determinations can give a precise answer as to the date of expected confinement. All too often, however, when the matter is of medical importance or in dispute, confusing answers can be obtained by these standard approaches to the calculation of term. In 1954 at the International Congress of Gynecology and Obstetrics, Lemberg-Siegfried and Stamm⁶ reported changes in the vaginal cytology at term which gave a more than 90 per cent correlation with the date of expected confinement. The present study is concerned with an effort to reduplicate these findings as to the reliability of vaginal cytology as a sign of the proximity of labor and delivery.

In 1893, Lataste⁷ reported his original observation that the vaginal epithelium underwent rhythmic changes in mammals. In 1917 Stockard and Papanicolaou,⁸ interested in studying sex determination in guinea pigs, revived and put to use the study of vaginal cytology to follow the changes in their laboratory animals, and the technique soon outgrew the individual experiment.

In 1925 Papanicolaou⁹ reported optimistic but inconclusive studies attempting to diagnose early pregnancy by vaginal smear technique. These observations were extended in 1946¹⁰ but at no point have there been consistent studies of the changes in the last few weeks of pregnancy nor have there previously been attempts to determine the day of labor from changes in the vaginal epithelium.^{11, 12}

Cytologic studies of the last weeks of pregnancy have shown changes during the last few days as indicated in Fig. 1. Throughout the earlier weeks of pregnancy desquamation of vaginal epithelial cells has been in plaques and sheets (Fig. 2). Between six days and one day prior to term these begin to thin out, although retaining a dense appearance, and on the day prior to delivery the desquamation of the vaginal epithelial cells is in the form of discrete individual cells (Fig. 3). The "navicular cells of pregnancy," seen early and throughout the gestation, grow fewer in number during these late days and are relatively infrequent on the day prior to delivery (Fig. 4).

The cytoplasm of the cells becomes progressively paler in its staining reactions and the nuclei become smaller and less well stained. There is a progressive increase in the percentage of leukocytes which is quite striking on the day prior to delivery, and the mucus on the cell spread increases progressively during the last week prior to delivery.

The term "the navicular cell of pregnancy" was coined by Papanicolaou. In 1925 in describing the cellular changes associated with pregnancy he used the term "boat-like" in referring to the elongated or concave cells, some more or less collapsed, and with a cytoplasm partially or totally plasmolyzed or vacuolized.⁹ In 1933 the term "navicular cell" was used and it was felt to be diagnostic of the presence of a pregnancy.¹³ In 1946, however, he¹⁰ pointed out that this cell can appear in other types of amenorrhea and is not as uniquely characteristic as at first had been hoped. In the patients considered in the present paper, however, the diagnosis of their pregnancy is not in doubt but rather the date of its termination.

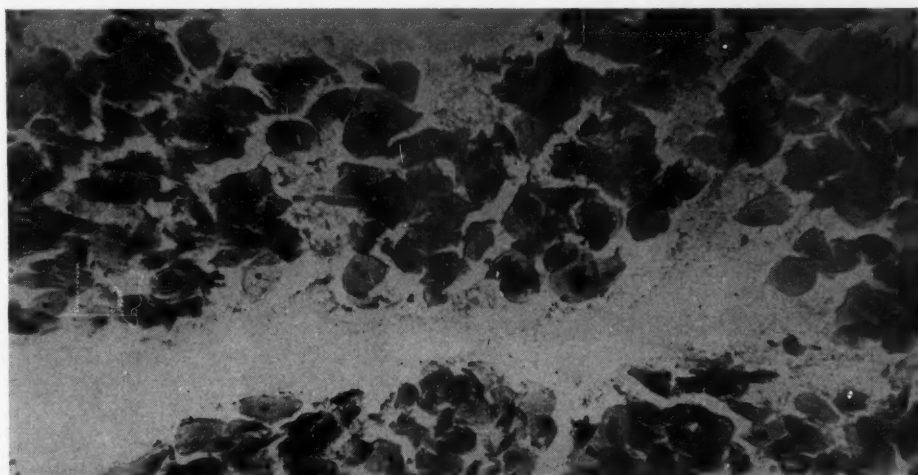


Fig. 2.—36 weeks' gestation. The cells are arranged in plaques and dense sheets and have a good cytoplasm and excellent cellular vitality. Leukocytes are few in number.

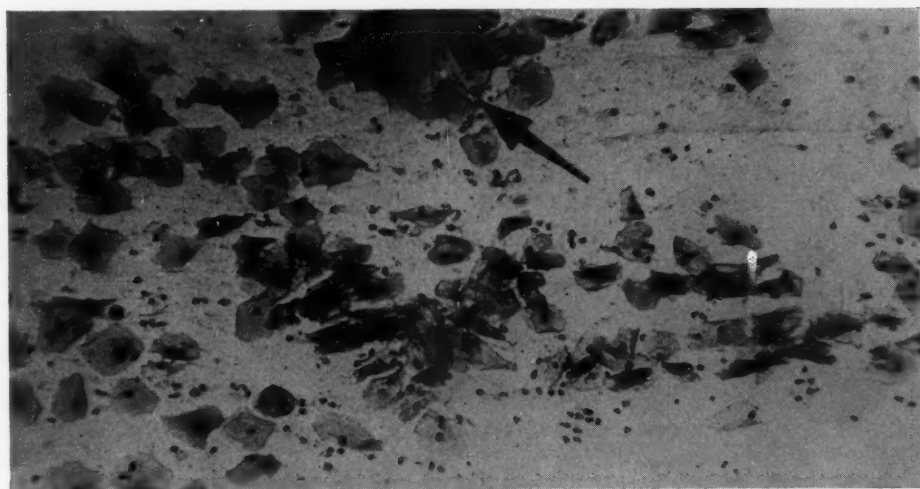


Fig. 3.—40 weeks' gestation. The cells may be in dense sheets or discrete. A good-to-pale colored cytoplasm is present. Navicular cells are present. Leukocytes are moderate in number.

One hundred and fifteen sets of smears were obtained on the same number of women during various stages of pregnancy, including term and post-

term, in labor, and in the immediate puerperium. The cytologic criteria which Lemberg had proposed were applied to these slides and a definite diagnosis made as to the stage in pregnancy or the puerperium of the individual patient. This diagnosis was then correlated with the stage of the patient's pregnancy at the time the smear was obtained. The correct week of gestation was determined after delivery, taking into account the size and weight of the baby, the actual date of delivery, as well as the history and progress of the entire pregnancy. The cells for the studies were obtained both by vaginal swab and by pipette aspiration of the posterior fornix in each patient and were stained by Shorr's¹⁴ technique.

The highest degree of accuracy in the diagnosis of these slides was obtained in the postpartum period associated with increased fragmentation of cells and the appearance of the "postpartum cell"¹² (Fig. 5).

This, however, is not clinically of assistance, and in the remainder of the determinations taken during pregnancy or while the patient was in labor the accuracy was considerably less (Table I). Assuming that the incorrect diagnostic readings are misleading and the doubtful diagnoses are at best of no help, the diagnoses were correct (excluding the postpartum determinations) in 73 per cent of cases.

TABLE I. RESULTS OF VAGINAL CYTOLOGY CORROBORATING PERIOD OF GESTATION

| | CORRECT | DOUBTFUL | INCORRECT | TOTAL |
|------------------------|---------|----------|-----------|-------|
| Post partum | 17 100% | 0 | 0 | 17 |
| Labor | 6 60% | 2 | 2 | 10 |
| Post "term" deliveries | 14 77% | 1 | 3 | 18 |
| 40 weeks' gestation | 24 73% | 2 | 7 | 33 |
| 36 weeks' gestation | 12 75% | 1 | 3 | 16 |
| 12 weeks' gestation | 16 76% | 4 | 1 | 21 |
| Total | 89 77% | 10 | 16 | 115 |

In the 14 patients whose histories would indicate that they were 41 weeks or more pregnant at the time the smear was obtained and whose babies showed some of the stigmas of postmaturity, the percentage of accuracy of the cytologic study reached its peak (77 per cent). While such figures would indicate the possible advantage of definite diagnosis of "at term" in a disputed case of postmaturity, the high percentage of doubtful and incorrect readings would probably not make this a test of wide applicability at the present time.

Lemberg-Siegfried also reported the observation that, if the administration of 20 mg. of estradiol increased the acidophilic reaction of the cells with a general regression in cellular vitality, then labor and delivery were imminent. Accordingly, a group of 5 patients at between 36 and 38 weeks of pregnancy were administered 20 mg. of sodium estrone sulfate intravenously. Smears were taken prior to the administration of the estrogen and again in 48 hours. These patients showed a slight but definite increase in acidophilic cells and a relative decrease in navicular cells. No appreciable change was seen in cellular vitality. All slides upheld the criteria that the patients were not at "term" both before and after sodium estrone sulfate was given.

These findings confirm that there are changes in the vaginal cytology during the last week of pregnancy that are fairly characteristic of the approach of labor and delivery. The present study cannot confirm, however, that these changes are observed in more than 90 per cent of the cases, and it is believed that the observed degree of accuracy of about 75 per cent makes it unlikely that this test will be in any sense routine in its application.

During the same period that vaginal smears were being employed to determine the stage of pregnancy and whether or not the patients were at term, two control series were followed: (a) 114 women whose menstrual history carefully correlated with the date they delivered; and (b) 100 women at or near term in whom the fetal weight was estimated by abdominal palpation during labor and subsequently compared with the determined weight of the newborn baby.



Fig. 4.—Labor. The cell pattern shows discrete cells, all of which show a pale cytoplasm with a decreased-to-absent number of navicular cells. The general cellular vitality is poor and an increased number of leukocytes are seen.

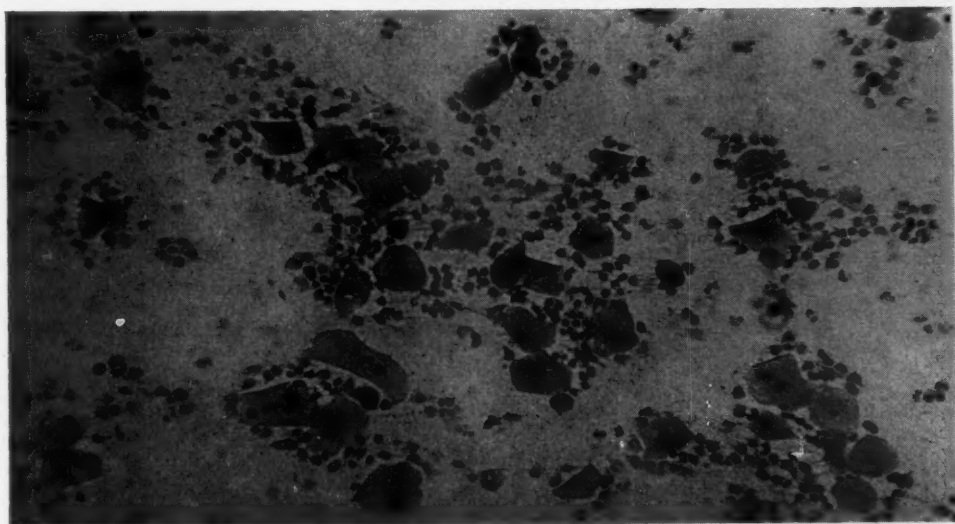


Fig. 5.—Post partum. The cells are arranged in plaques or dense sheets. The navicular cells may or may not be present. The cytoplasm and cellular vitality are good. Leukocytes are present in varying numbers. Acidophilic cells are present in increased numbers. The outer basal-cell types are numerous.

(a) *Menstrual History.*—The 114 patients were selected as being at term by fetal size and appearance, the date of quickening, the first determination of fetal heart sounds and the sequential abdominal measurements of uterine growth. In 44 of the 114 patients the menstrual history agreed with the ultimate date of delivery plus or minus one week. In other words, relying on menstrual his-

tory alone, the correct delivery date (within 14 days) could have been predicted in only 38.5 per cent of the pregnancies. Forty-five of the women delivered earlier than their menstrual history would indicate (an average of 17 days), while 25 patients (22 per cent) averaged more than 15 days late, and represent the group that would raise the question of postmaturity.

(b) *Antepartum Estimation of Fetal Size.*—At each antepartum visit after the fifth month and through labor, estimations of fetal weight were made on the basis of the findings at abdominal palpation. The weight of the newborn, plus or minus 240 grams, agreed with the last estimate prior to delivery in 59 per cent of the cases. In 26 per cent of the patients the estimate was high, while in the remaining 15 per cent the estimated weight was low. This technique in trained hands actually is of value chiefly in predicting the relationship between the fetus and the pelvis. In the review of these records, however, it became apparent that in many cases *sequential* estimations of fetal size gave an accurate picture of the progress of the pregnancy, particularly in the cases of postmaturity in which fetal size diminished.

Summary and Conclusions

The cytologic criteria proposed for the determination of date of delivery from vaginal smears were applied to 114 patients in varying stages of pregnancy and labor with an over-all accuracy of 73 per cent. The postpartum cellular picture is more characteristic although clinically less useful.

While in this clinic such a degree of accuracy exceeds that obtained from menstrual history alone, or from the estimation of fetal size alone, it is felt that the sizable margin of error together with the comparative difficulty of execution would keep this test from routine application. In disputed cases of postmaturity a positive "at term" diagnosis could be of assistance.

We wish to express our appreciation to Dr. James L. Reagan for the staining in his laboratory of the slides involved in this study.

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Discussion

DR. FRANK W. PEYTON, Lafayette, Indiana.—Obstetrics has reached the level where delivery time should be thought of for the welfare of the infant rather than the

convenience of parents, physicians, and friends. Words such as "delivery date" and "labor" are maternal, while "prematurity," "term," and "postmaturity" apply to the condition of the infant. Though in making these distinctions I may appear to be belaboring the obvious, I believe that the attitudes represented by the two sets of terminologies may be significant.

We have just heard the findings of vaginal cytology in the last stages of pregnancy. Some physicians already feel that the time, effort, and expense involved in applied cytology are impractical; and the addition of the smear under discussion to the other procedures involved would increase their woes. Vaginal instrumentation close to delivery with its attendant potential contamination, coupled with poorly trained "smear viewers," would make practicality more questionable. It seems from what Dr. Barnes has told us that, in the absence of absolutely definitive signs, the objectivity of any viewer could contribute little to the attending obstetrician. This closes my discussion of the negative aspects.

Dr. Barnes mentioned his findings of the postmature smear only in passing. Since he reported this phase as the peak of accuracy, and since it is so applicable to the solution of a problem, I would like to know more about it. What did the three inaccurate smears show? Another question I would like to ask is, would it be worth while to use the 75 per cent test as an adjunct in estimating when a baby should be born? General surgeons, I am told, still use leukocytosis as an aid in determining appendicitis. My last question is, do you consider the interpretation of this smear hard to learn?

I wish to state that this paper provokes and renews interest in an unsolved problem. It was valuable to have existing clinical techniques re-evaluated.

DR. E. STEWART TAYLOR, Denver, Colo.—Considering the possibility that hormonal changes which may occur prior to the onset of labor would be reflected in the cytology of the urinary sediment, we¹ obtained weekly urine specimens from two to four weeks before term up to delivery in 14 patients. Up to a week before delivery, these smears showed merely the characteristics of the last trimester of pregnancy, but specimens obtained within the last seven to eight days showed several characteristic changes. There was a definite increase in cellularity with the presence of sheets of navicular and superficial cells. Most striking, however, was the appearance of variable-sized and irregularly shaped cells with large vesicular nuclei, often two or three to a cell. The larger cells exceeded the superficial cells in size. The cytoplasm stained a deep pink to orange or sometimes blue. Usually it was homogeneous, though occasional vacuoles were observed. In the smaller cells the nuclei exceeded half the cell area. These cells were found in moderate numbers in the last week of pregnancy, increased greatly after the onset of labor, and persisted after delivery. They conformed to the description by Papanicolaou of what he called postpartum cells. Such cells were found in the vaginal smears taken after delivery and up to ten days post partum.

In urinary smears obtained twenty-four to forty-eight hours prior to the onset of premature labor in 2 patients, these so-called postpartum cells were also observed.

Apparently an extensive desquamation of the epithelium of the urinary tract precedes and accompanies the onset of labor. Such a phenomenon has evidently not been observed in the human vaginal epithelium, though Davis and Hartman² reported that in monkeys almost the entire vaginal epithelium is desquamated prior to the onset of labor.

A smear was examined from a patient 3½ months pregnant who expelled a hydatidiform mole a week later. It resembled the average cytologic picture of this gestation period. High chorionic gonadotropin levels which in this patient exceeded 200,000 rat units per liter of urine apparently do not directly affect the cytology of the urinary tract.

The alterations in the urinary smear preceding labor are interesting in view of what is known about hormonal changes at this period. Smith, Smith, and Schiller³ have reported a gradual fall in estrogen secretion during the last two weeks of pregnancy which becomes precipitous at the onset of labor. Just as the premenstrual smear shows an increased desquamation with the fall in hormone levels, so the apparent desquamation of urinary tract epithelium observed in the last week of pregnancy may well be due to a gradual fall in estrogen beginning about two weeks before term and, as the estrogen falls precipitously at

the onset of labor, so does the shedding of the epithelium of the urinary tract increase. Whatever the hormonal change, the findings in the urinary smear seem to indicate that some alteration in hormonal balance precedes and accompanies the onset of labor.

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DR. ZUSPAN (Closing).—The three inaccurate smears referred only to the fact that we were unable to make a diagnosis of pregnancy at term. In other words, these particular slides showed the patients to be probably somewhere around 36 weeks' gestation as far as we could tell.

The question also was asked, would this task be a useful adjunct in determining when the baby should be born? I believe that probably in certain selected instances this might be true. We can probably think of the estimated date of confinement as a converging funnel through which we pass both the clinical and the laboratory adjuncts to determine certain questions in relation to when we think the baby should be born. I think this would be most useful in questions of postmaturity of those who do believe in this syndrome.

We did not know the particular gestation of the patient when we were reading the slides, and we tried to be as honest as we possibly could in reading them. We went back and recompared the readings of the slides with the known gestations at a later date.

I do not believe the interpretation of the slides was too difficult. At first it seemed somewhat confusing, but the more time spent in looking at the slides, the more obvious the answer became. The gross appearance of the slide could almost determine the actual relative date of gestation. In the patients who were at term you could hold the slide up to the light and it would give a characteristic almost dirty appearance, whereas the slides in earlier gestation would be much cleaner.

It is interesting to hear that there are changes in the urinary tract and cellular patterns which also are consistent with the vaginal changes. Why these changes take place, I have no idea. I do not believe any explanation has as yet been offered.

THE ACTION OF MAGNESIUM SULFATE ON CEREBRAL CIRCULATION AND METABOLISM IN TOXEMIA OF PREGNANCY*

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THE use of magnesium sulfate dates back to 1618 when Henry Wickes, a farmer, discovered the spring at Epsom in southern England.¹ These waters contained large amounts of magnesium sulfate, the epsom salts of that day as well as this. At first they were used only externally to "bathe open sores and painful affections." The third Lord Dudley North² soon became acquainted with the effects of the waters when taken internally, and in 1645 he wrote a treatise extolling the virtues of this medication. Thereafter Epsom became one of the most fashionable spas in the world and magnesium sulfate became one of the most important medications in the physicians' armamentarium.

After over 200 years of use only as a cathartic, hydragogue, or in local fomentations, it was recognized at the turn of the last century that, in addition, magnesium sulfate possessed sedative qualities. In 1905³ and 1906⁴ the first reports were published on its efficacy in treating the convulsions of tetanus. A few articles then appeared in the foreign literature^{5, 6} reporting its anticonvulsant properties in eclampsia. In this country the first notable studies of the effects of magnesium sulfate in toxemia of pregnancy were those of Dorsett, Lazard, and Alton and Lincoln. Dorsett,⁷ a member of this society, reported the value of magnesium sulfate when given intramuscularly. Lazard⁸ administered the drug intravenously, and Alton and Lincoln⁹ gave it intrathecally. Since then a great many favorable reports have appeared and, at the present time, magnesium sulfate is widely used in the therapy of eclampsia and severe pre-eclampsia.

During our investigations of the brain in toxemia of pregnancy, a number of sedatives and vasodilators commonly used empirically were studied.¹⁰⁻¹⁵ This was done in an attempt to understand more fully the interplay between the effects of toxemia itself on the brain and the effects of symptomatic treatment. We felt that this study might well provide a more intelligent basis on which to treat the patient.

This presentation represents the last of these studies: the effects of magnesium sulfate on cerebral circulation and metabolism in toxemia of pregnancy.

Method

The nitrous oxide method was used. This method has been described repeatedly in recent literature.¹⁶ Venous blood from the internal jugular vein

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and arterial blood from the femoral artery are withdrawn simultaneously while the patient breathes a mixture of 15 per cent nitrous oxide, 21 per cent oxygen, and 64 per cent nitrogen for a period of ten minutes. Mean arterial blood pressure is measured directly from the femoral artery with a damped mercury manometer. Blood gas analyses of nitrous oxide, oxygen, and carbon dioxide are made with the Van Slyke-Neill apparatus.

As previously described,¹⁷ cerebral blood flow (CBF) is measured in cubic centimeters per 100 grams of brain per minute. Cerebral oxygen metabolism (CMR_{O₂})* may then be calculated in cubic centimeters of oxygen utilized per 100 grams of brain per minute, and cerebral vascular resistance (CVR)† in millimeters of mercury pressure per cubic centimeter of blood per 100 grams of brain per minute. The respiratory quotient (RQ) is calculated by computing the relationship between the oxygen uptake by the brain and the amount of carbon dioxide given off.‡

Thirty investigations were carried out on 15 women in the third trimester of gestation with toxemia of pregnancy. Nine were patients with pre-eclampsia per se and 6 had acute toxemia superimposed on pre-existing mild essential hypertension. No therapy except ordinary bed rest was given for at least 12 hours before the control investigation (C). After the first determinations were made, the patient was immediately given 20 c.c. of 10 per cent solution of MgSO₄ intravenously over a period of five minutes. As soon as the maximum effect of the drug was attained, the second observation (E) was made. This was usually between 5 and 15 minutes. Aside from hot flashes and an occasional wave of nausea, there were no ill effects from the medication.

TABLE I. EFFECT OF MAGNESIUM SULFATE ON BLOOD GASES

| PATIENT | DIAGNOSIS | (A-V)O ₂ | | (V-A)CO ₂ | | ARTERIAL | | | | INTERNAL JUGULAR | | | |
|-------------|---------------|---------------------|-----|----------------------|-----|------------------|------|------------------|------|------------------|------|------------------|------|
| | | (VOL. %) | | (VOL. %) | | O ₂ | | CO ₂ | | O ₂ | | CO ₂ | |
| | | C* | E* | C | E | CONTENT (VOL. %) | | CONTENT (VOL. %) | | CONTENT (VOL. %) | | CONTENT (VOL. %) | |
| C. B. | Hypertensive | 6.4 | 6.4 | 6.4 | 6.4 | 16.0 | 15.8 | 47.6 | 47.1 | 9.6 | 9.4 | 54.0 | 53.5 |
| E. B. | Pre-eclampsia | 6.3 | 6.3 | 6.2 | 6.3 | 13.8 | 14.0 | 40.5 | 40.6 | 7.5 | 7.7 | 46.7 | 46.9 |
| B. B. | Pre-eclampsia | 6.5 | 6.4 | 6.4 | 6.4 | 15.6 | 15.8 | 41.9 | 42.0 | 9.1 | 9.4 | 48.3 | 48.4 |
| D. S. | Pre-eclampsia | 6.6 | 6.6 | 6.7 | 6.6 | 14.3 | 14.1 | 40.8 | 40.7 | 7.7 | 7.5 | 47.5 | 47.3 |
| R. D. | Pre-eclampsia | 6.8 | 6.8 | 6.9 | 6.8 | 16.2 | 16.4 | 43.9 | 44.1 | 9.4 | 9.6 | 50.8 | 50.9 |
| E. C. | Pre-eclampsia | 6.6 | 6.7 | 6.8 | 6.8 | 15.8 | 15.7 | 41.6 | 41.6 | 9.2 | 9.0 | 48.4 | 48.4 |
| J. S. | Pre-eclampsia | 6.4 | 6.5 | 6.6 | 6.6 | 15.0 | 15.2 | 46.2 | 46.4 | 8.6 | 8.7 | 52.8 | 53.0 |
| J. D. | Hypertensive | 6.6 | 6.6 | 6.7 | 6.6 | 15.9 | 16.1 | 44.3 | 44.4 | 9.3 | 9.5 | 51.0 | 51.0 |
| L. M. | Pre-eclampsia | 6.7 | 6.7 | 6.6 | 6.6 | 14.2 | 14.0 | 39.6 | 39.5 | 7.5 | 7.3 | 46.2 | 46.1 |
| E. W. | Pre-eclampsia | 6.5 | 6.6 | 6.5 | 6.5 | 11.8 | 10.8 | 36.3 | 36.0 | 4.5 | 4.2 | 42.8 | 42.5 |
| V. W. | Hypertensive | 6.4 | 6.5 | 6.6 | 6.6 | 16.3 | 16.5 | 42.9 | 43.4 | 9.9 | 10.0 | 49.5 | 50.0 |
| M. T. | Hypertensive | 6.5 | 6.5 | 6.5 | 6.5 | 16.9 | 16.8 | 46.7 | 46.5 | 10.4 | 10.3 | 53.2 | 53.0 |
| C. B. | Pre-eclampsia | 6.5 | 6.6 | 6.6 | 6.6 | 14.7 | 15.0 | 39.8 | 40.6 | 8.2 | 8.4 | 46.4 | 47.2 |
| S. D. | Hypertensive | 6.8 | 6.8 | 6.7 | 6.7 | 15.3 | 15.3 | 39.9 | 39.9 | 8.5 | 8.5 | 46.6 | 46.6 |
| E. W. | Hypertensive | 6.7 | 6.8 | 6.8 | 6.8 | 14.3 | 14.4 | 45.9 | 46.0 | 7.6 | 7.6 | 52.7 | 52.8 |
| Mean Values | | 6.5 | 6.6 | 6.6 | 6.6 | 15.1 | 15.0 | 42.5 | 42.6 | 8.5 | 8.5 | 49.1 | 49.2 |

*C = Control flow.

E = After medication.

Results

The blood gas determinations of oxygen and carbon dioxide are shown in Table I. The administration of MgSO₄ did not affect the arteriovenous oxygen

$$*CMR_{O_2} = CBF \times \frac{(A - V)O_2}{100}$$

$$\dagger CVR = \frac{MABP}{CBF}$$

$$\ddagger RQ = \frac{(V - A) CO_2}{(A - V) O_2}$$

difference, the venous-arterial carbon dioxide difference, or the values for femoral arterial and internal jugular venous oxygen and carbon dioxide.

Table II depicts the mean arterial blood pressure, cerebral blood flow, cerebral oxygen metabolism, cerebral vascular resistance, and respiratory quotient of the brain before and after MgSO_4 .

Mean arterial blood pressure was lowered from 119 to 113 mm. Hg. This is statistically significant ($p < 0.01$). Normal values usually are in the range between 78 and 90 mm. Hg and it is evident that in spite of MgSO_4 therapy, hypertension was still present.

Cerebral blood flow increased from 54 to 58 c.c. per 100 grams of brain per minute. This too was a significant rise ($p < 0.01$).

Cerebral oxygen metabolism increased from 3.6 to 3.8 c.c. per 100 grams of brain per minute ($p < 0.01$).

Cerebral vascular resistance diminished from an average of 2.2 to 2.0 mm. Hg per cubic centimeter per 100 grams brain per minute after intravenous administration of MgSO_4 . This lessening of cerebral vascular tone was a consistent finding in this group of patients which made it highly significant statistically ($p < 0.001$). On the other hand, the vasodilatation brought about was not sufficient to restore the normal tone of the cerebral vessels (1.6 mm. Hg per cubic centimeter per 100 grams of brain per minute).

The respiratory quotient of the brain was unaffected and remained at unity.

TABLE II. EFFECT OF MAGNESIUM SULFATE ON CEREBRAL FUNCTION

| PATIENT | DIAGNOSIS | CEREBRAL | | | | | | | | | |
|-------------|---------------|-------------------|------|---|-----|---|------|--|------|------|------|
| | | MABP* (MM. HG) | | CBF (C.C./100 GM. BRAIN/ MIN.) | | CMR _{O2} (C.C./100 GM. BRAIN/ MIN.) | | CVR (MM. HG/ C.C./100 GM. BRAIN/ MIN.) | | RQ | |
| | | | | | | | | | | | |
| | | C | E | C | E | C | E | C | E | C | E |
| C. B. | Hypertensive | 136 | 129 | 52 | 60 | 3.3 | 3.8 | 2.6 | 2.2 | 1.00 | 1.00 |
| E. B. | Pre-eclampsia | 126 | 116 | 52 | 56 | 3.3 | 3.5 | 2.4 | 2.1 | 0.98 | 1.00 |
| B. B. | Pre-eclampsia | 99 | 95 | 55 | 55 | 3.6 | 3.5 | 1.8 | 1.7 | 0.98 | 1.00 |
| D. S. | Pre-eclampsia | 109 | 121 | 50 | 56 | 3.3 | 3.7 | 2.2 | 2.2 | 1.01 | 1.00 |
| R. D. | Pre-eclampsia | 114 | 127 | 58 | 64 | 3.9 | 4.4 | 2.0 | 2.0 | 1.01 | 1.00 |
| E. C. | Pre-eclampsia | 108 | 91 | 61 | 62 | 4.0 | 4.2 | 1.8 | 1.5 | 1.03 | 1.01 |
| J. S. | Pre-eclampsia | 109 | 99 | 53 | 50 | 3.4 | 3.2 | 2.1 | 2.0 | 1.03 | 1.01 |
| J. D. | Hypertensive | 161 | 150 | 54 | 59 | 3.6 | 3.9 | 3.0 | 2.5 | 1.01 | 1.00 |
| L. M. | Pre-eclampsia | 103 | 96 | 50 | 55 | 3.4 | 3.7 | 2.1 | 1.7 | 0.98 | 0.98 |
| E. W. | Pre-eclampsia | 100 | 90 | 53 | 60 | 3.5 | 4.0 | 1.9 | 1.5 | 1.00 | 0.98 |
| V. W. | Hypertensive | 137 | 130 | 57 | 51 | 3.7 | 3.3 | 2.4 | 2.5 | 1.03 | 1.01 |
| M. T. | Hypertensive | 98 | 88 | 59 | 62 | 3.8 | 4.0 | 1.7 | 1.4 | 1.00 | 1.00 |
| C. B. | Pre-eclampsia | 113 | 101 | 58 | 66 | 3.8 | 4.4 | 2.0 | 1.5 | 1.01 | 1.00 |
| S. D. | Hypertensive | 154 | 149 | 47 | 57 | 3.2 | 3.9 | 3.3 | 2.6 | 0.98 | 0.98 |
| E. W. | Hypertensive | 111 | 105 | 51 | 59 | 3.4 | 4.0 | 2.2 | 1.8 | 1.01 | 1.00 |
| Mean Values | | 119 | 113† | 54 | 58† | 3.6 | 3.8† | 2.2 | 2.0† | 1.00 | 1.00 |

*MABP = Mean arterial blood pressure

†p < 0.01.

‡p < 0.001.

Comment

In toxemia of pregnancy, as in any disease where we are utterly dependent upon empiric therapy, it has been necessary to evaluate treatment purely from the clinical point of view and this at times has led to error. Today, with new quantitative methods for measuring basic functions of important organs, it has become increasingly possible for us to determine which symptomatic therapy most effectively relieves the pathophysiology present and which may be detrimental.

Magnesium sulfate lowers blood pressure, relieves cerebral vasospasm, increases cerebral blood flow, and augments oxygen utilization by the brain. These changes are the direct opposite of those brought about by toxemia of pregnancy. Pre-eclampsia raises blood pressure and increases cerebral vascular tone while eclampsia also depresses cerebral oxygen metabolism.

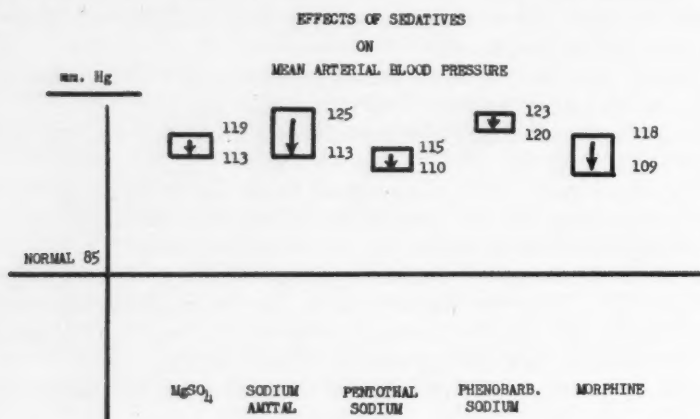


Fig. 1.

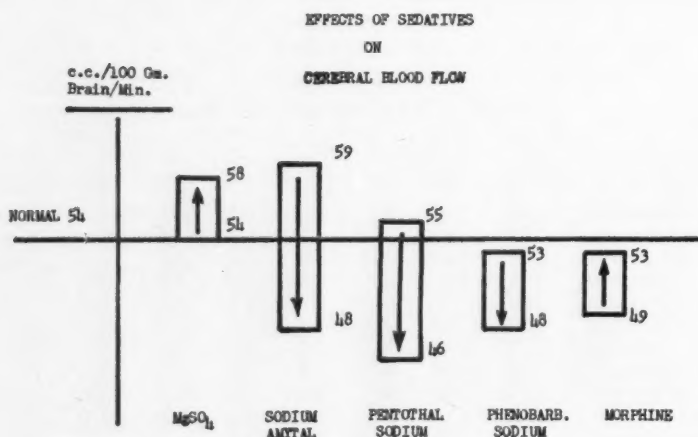


Fig. 2.

Furthermore, magnesium sulfate is an excellent anticonvulsant.^{3, 18, 19} Pritchard's²⁰ recent work has re-emphasized this fact, and he has pointed out that, when given in large dosage, this agent does not markedly alter renal plasma flow or glomerular filtration rate, nor does it depress the fetus or interfere with uterine contractions.

The exact mechanisms of the sedative and the vasodilator activity of magnesium sulfate are not completely understood.^{21, 22} It is known that a central depression of the brain takes place, but this depression is not marked except in dosages beyond the therapeutic range. The peripheral obtunding effect at the neuromuscular junction is probably of greater importance. Therefore, the anticonvulsant action of magnesium sulfate is associated with lessened neuro-

genic reactivity without deep depression. The rather mild vasodilator action of the drug is reputedly due to direct peripheral effect on the walls of the small blood vessels.

How do other sedatives and vasodilators compare with magnesium sulphate as to their effects upon cerebral function? (Figs. 1 to 6.)

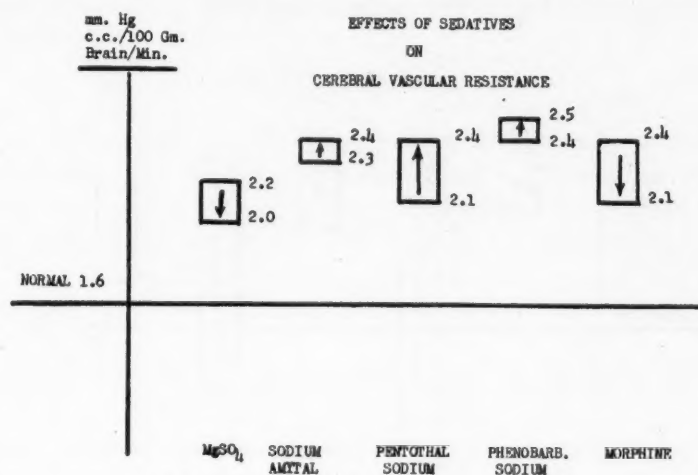


Fig. 3.

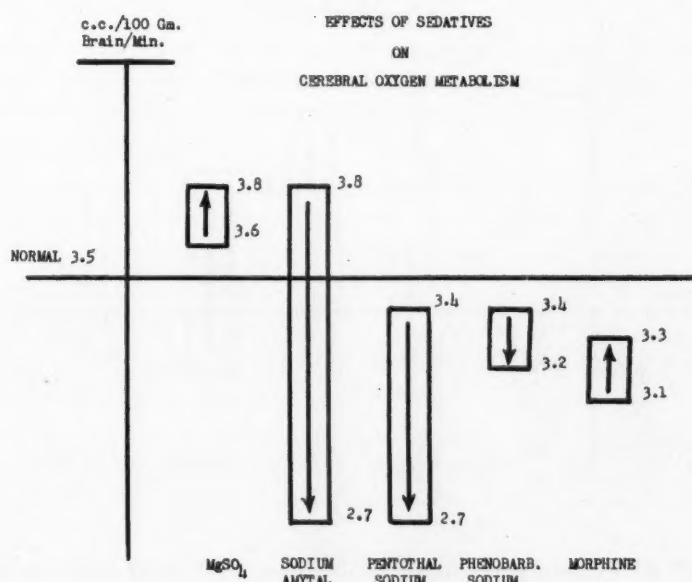


Fig. 4.

Using the same methods of investigation, we found that morphine sulfate and phenobarbital sodium given intramuscularly affect the brain least. Cerebral blood flow and oxygen metabolism remain normal, but cerebral vascular spasm is unrelieved. The intravenously administered barbiturates, on the other hand, such as sodium Amytal and Pentothal sodium, cause cerebral ischemia and

marked depression of cerebral oxygen metabolism. Cerebral vasoconstriction is either unaffected or made worse by these drugs. Eclampsia itself brings about much the same type of anoxia and disruption of physiology. These studies strongly suggest, therefore, that magnesium sulfate is superior to other sedatives in the therapy of pregnancy toxemia.

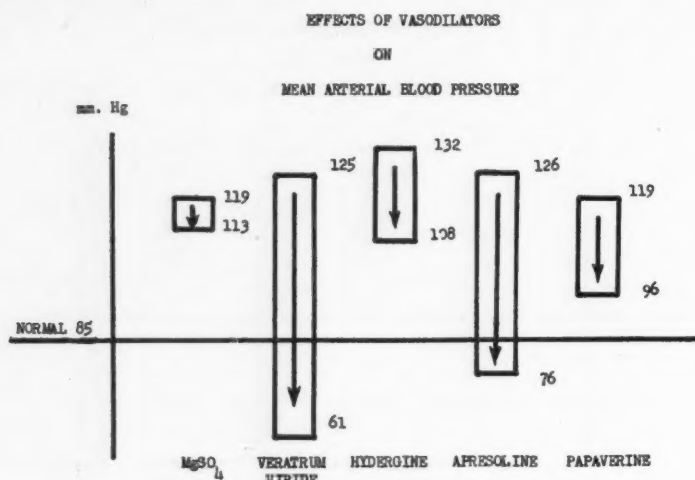


Fig. 5.

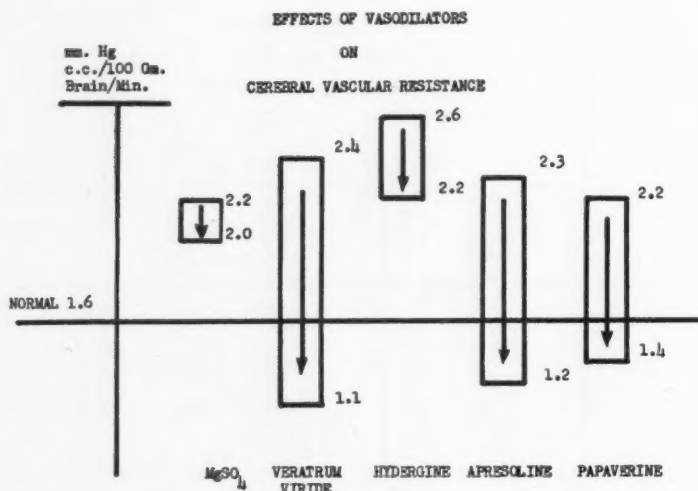


Fig. 6.

A number of well-known vasodilators have also been evaluated as to their effect on the brain in toxemia of pregnancy. Magnesium sulfate exerts a much less dilating effect on the cerebral vessels than do papaverine, Hydergine, Apresoline, Unitensin (cryptenamine), or crude *Veratrum viride*. For example, the *Veratrum viride* substances lowered cerebral vascular resistance¹⁵ over 100 per cent (2.4 mm. Hg to 1.1 mm. Hg) as compared with the 10 per cent decrease when magnesium sulfate was used. Cerebral circulation and metabolism are not compromised by these vasodilators or MgSO₄.

It appears logical, therefore, not only to make use of magnesium sulfate, but also to utilize vasodilator therapy of the proper type²³ in severe toxemia of pregnancy. This should insure protection against convulsions and hypertensive-vasospastic complications without causing maternal or fetal depression.

It is hoped that this investigation, which gives us a new understanding of an old therapeutic agent, will provide further impetus in the conquest of toxemia of pregnancy.

Summary

1. Studies of cerebral blood flow, cerebral vascular resistance, cerebral oxygen consumption, and respiratory quotient of the brain, as well as mean arterial blood pressure and the blood gases were made before and after intravenous administration of magnesium sulfate to 15 women with toxemia of pregnancy.

2. Magnesium sulfate significantly lowers mean arterial blood pressure, but not to normal levels.

3. Cerebral blood flow and oxygen utilization by the brain are slightly increased.

4. Cerebral vascular resistance is decreased to a notable degree but not to the point where normal cerebral vascular tone is restored.

5. A number of sedatives and vasodilators were compared and contrasted with the effects of magnesium sulfate on the brain.

A. Certain sedatives (intravenously administered barbiturates) depress cerebral oxygen metabolism in the same manner as does eclampsia. Cerebral blood flow is also decreased. None of the sedatives, other than magnesium sulfate, alleviated cerebral vasospasm.

B. All of the vasodilators studied relieved the increased cerebral vascular resistance without compromising cerebral circulation and metabolism.

6. It is concluded that magnesium sulfate with its exemplary action on the brain is a superior sedative and anticonvulsant in toxemia of pregnancy. Because its vasodilator action is not strong, it may be combined to great physiologic and therapeutic advantage with appropriate vasodilators when marked hypertension and vasospasm are present.

We wish to express our appreciation to June Mosenson and Claire Van Horn for their technical assistance and to Irwin, Neisler & Company, Ciba Pharmaceutical Products, Inc., and Sandoz Pharmaceuticals for their financial aid in this investigation.

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Discussion

DR. RICHARD D. BRYANT, Cincinnati, Ohio.—I have always maintained that experiments in therapeutics should be performed on patients suffering from the disease for which the therapeutic agent is intended, and that valid conclusions concerning these agents can be drawn from these experiments only, not from tests on animals or normal humans.

This discussant is not qualified to discuss CBF, MABP, or the significance of *p*, as used in this paper, being more at home in a contracted pelvis than a contracted arteriole. I accept without qualification the results reported by Dr. McCall, an astute, skilled, intellectually honest observer. The time devoted to his presentation today in no sense reflects the time and energy devoted to this study.

As pointed out by Dr. McCall, magnesium sulfate has been used for a good many years in one way or another, in the treatment of toxemia of pregnancy. It is rather surprising that so little is known of how, where, and why it acts in patients with pre-eclampsia and eclampsia. I believe one is justified in questioning evidence derived from animal experimentation, or clinical results in tetanus, strychnine poisoning, and so on.

I was sorry to hear Dr. McCall use the term "anticonvulsant." A convulsion is difficult to define, and an anticonvulsant still more difficult. No anticonvulsant properties of magnesium sulfate were revealed in this presentation, nor was a sedative action, as ordinarily interpreted.

Do not misunderstand me. I agree enthusiastically that magnesium sulfate has an irreplaceable part to play in the management of toxemia of pregnancy. I wonder if Dr. McCall made any observations on the duration of the effect of intravenously administered magnesium sulfate, and I hope that further future studies will confirm the effectiveness of intramuscular injections.

DR. MCCALL (Closing).—The word "anticonvulsant" was used. We were more or less quoting other people's reaction to this drug, and we felt we should mention that attribute of this drug as we evaluated it from this particular one.

As far as the duration of effect is concerned, as I mentioned, usually the greatest depression of blood pressure came about within five to fifteen minutes, with the intravenously administered drug in the amount we used.

We did study some patients who were given 10 Gm. of magnesium sulfate intramuscularly, and of course the effect was slower; but the effect upon cerebral function was approximately the same. We could not tell the difference, so we did not go further.

We feel clinically, however, that when we use this drug the intramuscular route is more logical.

RECONSTRUCTIVE OPERATIONS FOR OBSTRUCTION OF THE FALLOPIAN TUBES*

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WHAT might be termed the "renaissance" in the surgical approach to infertility occurred during the years immediately preceding chemotherapy and antibiotic therapy. Before this time surgical procedures were attempted in various forms but, because of the high percentage of failures, were largely discarded. Little that is new has been added recently to the surgical approach, yet operations previously discarded are receiving approbation. Little in the present paper is new and much has been said by others in previous studies, albeit under different conditions.

It was our endeavor to establish, after all else had failed, the continuity of the lumen of the Fallopian tube. Obstructions encountered were variable and included pathologic processes from without as well as inflammatory conditions from within. The duration and extent of such processes necessarily influenced the outcome of our endeavors. Our study included only those patients presenting themselves for treatment after the year 1944.

In a brief review of the literature one finds that Greenhill,¹ in 1937, reported a study of more than 800 cases based on a questionnaire. He was very pessimistic as a result of this study but the future does seem to offer more hope to these women. He reported 818 operations from which 54 (6.6 per cent) pregnancies resulted and of these 36 (4.4 per cent) came to delivery. In 1948, Weinstein² reported cases of 210 patients with infertility: 14 of these patients underwent surgical measures and 6 became pregnant; of the 6 pregnancies 3 resulted in abortions and 3 in full-term deliveries. In 1949, Rutherford³ reported in the literature one of the best series of cases in which operations were performed. There were 21 pregnancies resulting from 43 operations. He emphasized particularly that the successful results were obtained in cases in which the least surgical intervention was necessary. At times the only operative measure would be a lysis of adhesions or a probing of the tube; he was of the opinion that when the mucosal pattern had been disturbed or the blood supply interfered with, the prognosis was poor. In 7 cases in which lysis of adhesions only was done there were 4 pregnancies. Salpingostomy by the cuff method resulted in 11 pregnancies among 16 patients. In 11 cases of isthmie

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†The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

occlusion in which the tubes were probed there were 4 pregnancies; in 6 patients requiring uterotubal implantation there were 2 pregnancies. The ovaries were implanted to the submucosal region of the uterus 3 times but no pregnancies resulted. The average time from operation to pregnancies was 7½ months.

Bravo,⁴ in 1952, reported 40 cases; 29 patients underwent salpingolysis or salpingostomies and 9 pregnancies resulted; 11 patients underwent implantations and only 2 pregnancies resulted. Of the 40 patients, however, 23 had patent tubes postoperatively.

Ingersoll⁵ reported from Massachusetts General Hospital in 1949 that of 23 patients operated on between 1932 and 1947, 5 of whom had tubal implantations and 18 of whom had salpingostomies, 9 became pregnant; 3 in the first group and 6 in the latter.

Green-Armytage,⁶ in 1952, also had better results from tubal implantations, 6 of 17 patients delivering full-term babies. In addition to implanting the tubes, however, an obturator of stainless-steel wire or a ureteral catheter is threaded through the tubes and uterus into the vagina to be removed between the fifth and eighth days after operation. D'Ingianni and Fontenelle⁷ also used a cannula threaded through the tubes and 13 of 16 patients had patent tubes postoperatively. Five of these patients became pregnant. Mulligan and associates,⁸ in 1953, reported their use of polyethylene tubing in 69 patients. In 48 patients the tubes were reimplanted with 5 resultant pregnancies and in 21 patients fimbrial plastic operations were done, utilizing polyethylene tubing with 6 (24 per cent) patients becoming pregnant.

Material

Between the years 1945 and 1953, 26 patients at the Mayo Clinic fulfilled the criteria established in this study. The primary complaint of these persons was infertility, of either primary or secondary type. In each case, after careful medical and urologic work-up, the principal cause for infertility seemed to be tubal occlusion. Confirmatory evidence for such a preoperative diagnosis was obtained by studies utilizing air and contrast media. Preoperatively, attempts were made to assess, in each case, the presumptive cause of the obstruction. Such diagnoses included myomas, pelvic inflammatory disease, and endometriosis.

In 26 patients, 21 to 39 years of age, operation was advised. Fifteen of the 26 had previously undergone surgical procedures. Thirteen had had appendectomy, 6 had undergone unilateral salpingo-oophorectomy, one had undergone ligation of the remaining tube, and 3 underwent bilateral partial salpingectomy. All patients had been married for 2 to 17 years. Three of the 26 patients had had full-term pregnancies while 6 gave histories of spontaneous abortions. One patient had had an ectopic pregnancy which necessitated the removal of the Fallopian tube. Of the 5 patients who became pregnant after operation, 3 had had a previous pregnancy, though 2 of the previous conceptions had resulted in abortion. Therefore, the outlook does seem a little better when the patient has demonstrated an ability to conceive regardless of the outcome of conception. Eight of the 26 patients had received treatment previously for pelvic inflammatory disease.

Surgical Approach

Basically, one of three general surgical approaches was used: salpingostomy, with the formation of a cuff; implantation of the portion of the tube distal to the obstruction; or a combination of these procedures. In the interest of possible future childbearing, all existing pelvic pathologic conditions which could be remedied during the operation were corrected. Surgical procedures of this secondary nature included myomectomies, uterine suspension, excision of endometrial nodules, ovarian cystectomy, lysis of adhesions, and appendectomy.

Salpingostomy was chosen for 15 patients whose Fallopian tubes exhibited occlusion adjacent to or confined to the fimbrial end. In 5, salpingostomy in combination with tubal implantation was carried out for multiple obstructive elements, while in an additional 5 patients implantation alone was deemed advisable. One patient underwent an end-to-end anastomosis of the ampullary portion to effect continuity.

TABLE I. RECONSTRUCTIVE OPERATIONS IN CASES OF OBSTRUCTION OF THE FALLOPIAN TUBES

| OPERATION | PATIENTS | PATIENTS WITH TUBAL PATENCY PROVED BY INSUFFLATION | | NUMBER OF PATIENTS WHO BECAME PREGNANT AFTER OPERATION |
|---------------------------------|----------|--|---------------------|--|
| | | AFTER OPERATION | IN FOLLOW-UP PERIOD | |
| Salpingostomy | 15 | 10 | 6 | 1 (resulted in spontaneous abortion) |
| Implantation | 5 | 1 | 1 | 4 (primary pregnancies; 3 of these 4 also became pregnant later) |
| End-to-end anastomosis | 1 | 1 | 0 | None |
| Implantation plus salpingostomy | 5 | 4 | 2 | None |
| Total | 26 | 16 | 9 | 5 |
| | | (62 per cent) | (35 per cent) | (19 per cent) |

Postoperatively, all patients were placed on antibiotic therapy which was continued for 5 days. A Rubin test was attempted on all patients on the fourth or fifth day after operation. Vaginal bleeding was considered a contraindication to insufflation.

Of the 15 patients who underwent salpingostomy as a primary procedure, 14 were examined postoperatively by means of the Rubin technique. Ten of the 14 patients so examined showed normal tubal patency with moderate intraluminal pressures. The remaining 4 patients did not exhibit tubal patency in spite of several attempts with pressures to 200 mm. of mercury. One of the 4 patients, however, later reported tubal patency when examined under the supervision of her home physician 6 months after operation. Of the original 10 patients who showed normal tubal patency after operation, 4 have been found subsequently to have a recurrence of tubal occlusion. One patient in this group of 15 aborted spontaneously at 2 months.

The Rubin test showed that in the 5 patients who underwent tubal implantation as a primary procedure, only one proved to have patent tubes immediately after operation. It was most interesting, however, to note that in spite of the negative results to insufflation studies, 4 of these patients later became pregnant one or more times. To date (October, 1955), 7 full-term pregnancies are recorded from these women, the primary pregnancy occurring between 3 and 35 months after operation.

The one patient who underwent an end-to-end anastomosis was found to have normal tubal patency postoperatively, but follow-up studies by her home physician now show tubal occlusion. Pregnancy has not resulted.

Five patients had salpingostomy combined with tubal implantation. Four of the 5 had tubal patency immediately after operation and again within 2 weeks of the surgical procedure. Fifty per cent of these patients report non-patency in follow-up studies. Pregnancy has not resulted in any of these cases (Table I).

Technique

The surgical procedures were carried out by three surgeons and it was the policy of all three to do a dilatation of the cervix and an endometrial biopsy first. The biopsy furnishes added information on ovarian function while the dilatation of the cervix allows blood or irrigation fluid to pass readily through the uterus. In the occasional patient the surgeon may want to use methylene blue in the irrigating solution; by means of a vaginal sponge a quick check for the bluish discoloration can be made.

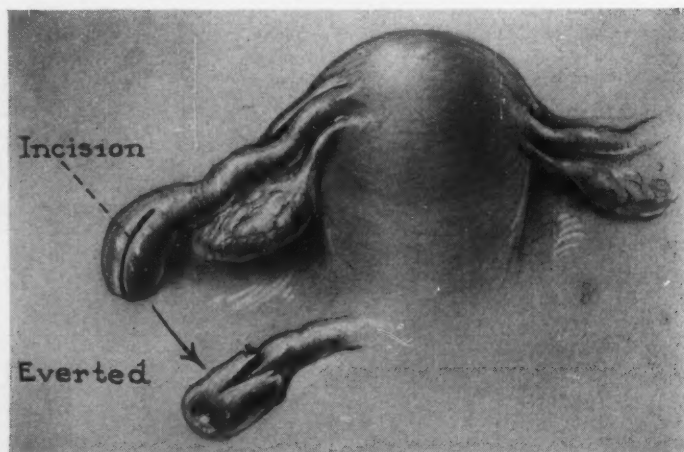


Fig. 1.—Salpingostomy with cuff operation for obstruction of the fimbrial end of the tube.

Salpingostomy consisted basically of splitting the end of the sealed tube, turning back the end as a cuff and suturing the mucosa to the outer wall of the tube with interrupted fine catgut sutures (Fig. 1). When the tubes are opened they are irrigated with saline solution to wash out any remaining oil or cellular debris and to demonstrate the patency of the uterine end of the tube. By the facility with which the fluid or air enters the tubal ostia the surgeon can ascertain whether or not it is entering the uterine cavity; occasionally it is even possible to clamp the lower portion of the uterus and, by irrigating one tube, have the fluid return through the opposite tube. In any case, once a passageway has been proved to exist and the end of the tube has been cuffed, all bleeding points are meticulously ligated and all raw surfaces are covered as completely as is possible.

If the fundus has been adherent in the cul-de-sac it should be held in a more normal anterior position by plicating the round ligaments anteriorly. Occasionally it is necessary to pass a suture from the hilum of the ovary to the peritoneum of the pelvic brim to prevent ovary and tube from becoming adherent to the deeper structures. Chemotherapy is generally employed by leaving 5 Gm. of sulfathiazole crystals in the abdomen before closure.

Polyethylene tubing (P.E. 10 to 250) is an excellent adjunct to use as a splint in holding the tubes or fimbria open. It was used only once in this series and without a pregnancy resulting, but this tubing has been utilized several times in the past 2 years. The end of the tubing should be passed through the uterus and out of the cervix or else the tubing should be threaded as far down the oviduct as possible and the end brought out through the anterior abdominal wall. Most reports in the literature suggest removing the tubing in 5 to 8 days; in one of our recent cases we did not remove the tubing for more than a month, but in others the tubing was removed in 6 to 7 days.

Fig. 2.

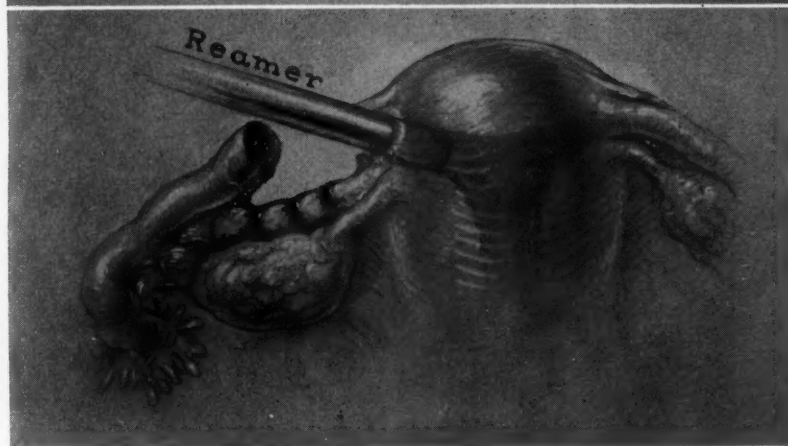


Fig. 3.

Fig. 2.—Obstruction of the uterine end of the tube. Division of the tube distal to the obstruction.

Fig. 3.—Obstruction of the uterine end of the tube; canal is established into the uterine cavity.

In only one case was an end-to-end anastomosis done for obstruction in the middle third of the tube. Probes easily passed this site after the anastomosis but pregnancy has not resulted. In a similar case, however, in 1954, the patient conceived within 3 months after operation.

The final method utilized to open the occluded oviducts was implantation of the proximal end of the distal portion of the tube into the uterine cavity. This method alone was used in 5 patients and in 5 others it was associated

with salpingostomy. When the uterus, tubes, and ovaries have been freed from all adhesions and brought to a relatively normal position in the pelvis, a pack is placed in the cul-de-sac to support the uterus (Figs. 2, 3, and 4). The tubes are then irrigated with saline solution to determine whether there is any obstruction outside the uterine wall; they are divided distal to any obstruction and their lumina again checked by freely washing through them. The medial end of the tube is split and fine catgut sutures, No. 3-0 or 4-0,

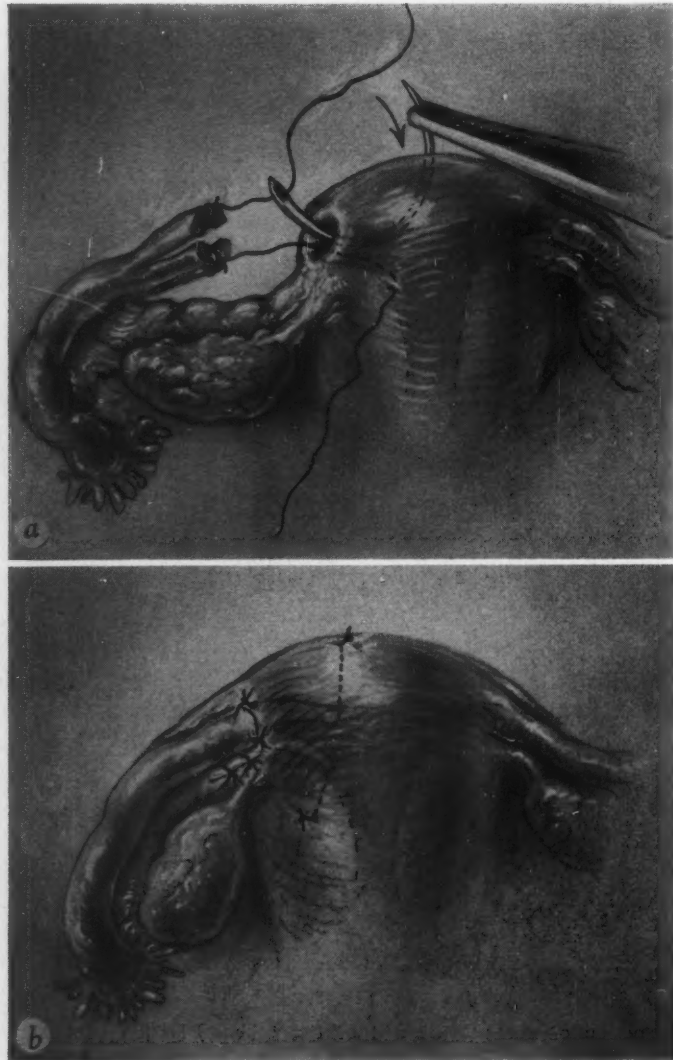


Fig. 4.—Obstruction of the uterine end of the tube. *a*, Placement of sutures for drawing the tube through the uterine wall into the endometrial cavity. *b*, Tube implanted and held with reinforcing sutures and defect of tubal mesentery closed.

stick-tied to each side. Care must be taken in these steps both to preserve as much length of the tube as possible and to maintain the arterial and venous vessels of the distal portion of the tube. An opening is made through the adjacent horn of the uterus into the endometrial cavity either by reaming out an opening with a 4.5 or 5.0 mm. punch, or by coring out a plug of tissue with a narrow-bladed scalpel. The blunt end of a large curved needle is passed

through the posterior uterine wall into the endometrial cavity and out of the newly formed opening. One suture on the end of the tube is threaded on the needle and pulled through the opening and out of the posterior wall. Similarly, the second suture is brought out the anterior uterine wall. By means of gentle traction on these sutures the end of the Fallopian tube is pulled through the horn of the uterus into the endometrial cavity. The sutures are tied and the position of the tube stabilized by several fine sutures from the serosa of the tube to the wall of the uterus. The defect in the mesentery and all raw surfaces are then closed and the tube is once more irrigated to wash out any blood that might have accumulated within it. Gentleness in the handling of all tissues is paramount and great care also should be taken to control even minor oozing. A small amount of blood about a fimbria might be just enough to seal the end of the tube and give a poor operative result.

Patients are ambulant 24 hours after operation and they are encouraged to walk, to move about, and to change their position frequently when in bed. Routine use of penicillin or penicillin and dihydrostreptomycin continues for several days postoperatively. Four patients were considered morbid, according to the postoperative temperature. A 35-year-old patient was thought to have bilateral phlebitis but anticoagulants were not necessary. A large hematoma developed in the subcutaneous tissue of another patient and necessitated her readmission to the hospital for drainage. There were no other complications. If vaginal bleeding does not occur, the Rubin test is attempted on the fourth or fifth day, and again 2 to 3 days later. The patients are urged to have repeated Rubin tests for the next month or two and are also advised to try to become pregnant within the next menstrual cycle.

Summary and Conclusions

During the years 1945 to 1953, inclusive, 26 patients at the Mayo Clinic fulfilled the criteria established for this study. The primary complaint was infertility, either primary or secondary in type. In each case tubal occlusion was established as the primary cause of the infertility. Prior to operation all patients and their husbands underwent a complete medical survey.

Four types of surgical approach were used: salpingostomy, tubal implantation, end-to-end anastomosis of the tube, and implantation plus salpingostomy. Salpingostomy was done in 15 patients; insufflation immediately after operation was positive in 10. In follow-up studies, however, tubal patency was noted in only 6. No full-term pregnancies resulted but one pregnancy resulted in spontaneous abortion.

Five patients underwent tubal implantation. The Rubin test gave positive results in only one of the 5 patients immediately after operation and within 2 weeks. Four primary pregnancies resulted, however, and 3 patients have had a second pregnancy.

An end-to-end anastomosis of the ampullary portion of the Fallopian tube was effected in one patient. Postoperative insufflation was positive but later examinations showed tubal occlusion. No pregnancies were reported.

A combination of implantation plus salpingostomy was effective in 5 patients. Successful tubal patency was established with the use of the Rubin technique in 4 patients immediately after operation, but the tubes in 50 per cent of this number later became obstructed. No pregnancies resulted.

Surgical procedures of secondary importance were carried out during the afore-mentioned procedures when, in the opinion of the surgeon, such steps would enhance the subsequent result. Secondary procedures included appendectomy, uterine suspension, ovarian cystectomy, lysis of adhesions, and removal of endometriomas. Each operation was preceded by cervical dilatation and uterine curettage. Morbidity was noted postoperatively in 4 patients.

A number of patients with tubal occlusion are candidates for definitive surgical procedures. In our cases the prognosis has been excellent when the fimbrial end of the tube was open and the obstruction was limited to the isthmie region. When the fimbriae have been occluded by previous pelvic inflammatory disease or when a hydrosalpinx is present, patency of the tubes can be established in a majority of the patients but, even so, few pregnancies result.

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Discussion

DR. FLOYD T. ROMBERGER, JR., Indianapolis, Ind.—A success rate of 80 per cent conceptions following tubal implantation, as reported by the authors, is excellent. On the other hand, their surgical procedures on the distal portion of the tubes yielded disappointingly poor results. This is the story usually reported by other investigators.

Green-Armytage in his discussion of the etiology of cornual obstruction, last year, reported a 40 per cent success rate after surgical correction. It was his feeling that, with improvements in technique and proper selection of patients, it should be possible to raise this to 60 or 70 per cent. He described a type of occlusion limited almost entirely to the cornual and adjacent isthmie portion. This was seen primarily in patients with histories of criminal abortions and low-grade puerperal or cervical infections. In these cases, the distal portions of the oviducts were normal.

Several writers have reported single cases where the anastomoses of previously ligated oviducts have been followed by conception. Here, also, one is dealing with normal ampullar ends. These groups confirm the experimental work on the rhesus monkey reported by Costello in 1950. He described the regeneration of the transected tube across a bridge of polyethylene tubing. His monograph reaffirmed the fact that both the ureter and Fallopian tube possess a similar growth urge, namely, the tendency to re-establish their lumina. Instances of this are seen in cases where recanalization has occurred following sterilization procedures in both the male and the female.

On the other hand, the physiological efficiency of the reconstructed ampullar end of the tube is reduced greatly as a result of the damage by previous infections. This probably is the explanation for the uniformly poor results obtained by plastic procedures on the distal portions.

The negative insufflation tests in 4 of the authors' 5 cases of implantation immediately postoperatively, and again within two weeks, were interesting. Conception occurred in 4 patients in this series. A similar situation, in so far as patency alone is concerned, was reported by Sovak in 1936. He explained this on the basis of a postsurgical tissue

reaction. One case was cited where occlusion still was present eight weeks postoperatively, but where patency developed following fourteen Elliott treatments. This therapy then was added to his postoperative routine.

It is interesting to note that polyethylene tubing or other splinting aids were not employed in the implantation group with its good success rate. This raises the question as to whether the use of these foreign materials is not a needless expenditure of energy and operating time for this type of obstruction.

Finally, with the exception of repeated gaseous insufflations, one reads little recently about the success or failures attained with conservative medical management. The emphasis has been on surgery. If all patients with occlusion were treated medically prior to operation, additional valuable information could be obtained. Perhaps a few candidates might be eliminated from the surgical group, while those who undergo operation might be benefited by the inclusion of one or more of these medical measures.

DR. PRATT (Closing).—These patients of ours have been well screened. They have had a complete medical work-up, and where there was any doubt as to the occlusion (and in many cases where there was no doubt) the patients have been advised to continue along conservatively, perhaps with pelvic heat, with diathermy, for a period of months. But when everything else has failed we have gone back to surgery, trying to establish a new lumen through the tubes.

I do not believe we emphasized the fact that we use antibiotics routinely after surgery. Generally we use 5 Gm. of sulfathiazole in the pelvis, if the patient has no sensitivity to sulfonamides. We put them on penicillin postoperatively for the next four or five days. We have not used pelvic heat routinely. Perhaps we should, particularly if the oviduct is not open immediately. That has been pointed out in the past to be effective, and in at least one of our patients whose Rubin test was negative immediately after operation, and for the first three or four times, some four months later her own physician reported that air was passing freely through the tubes.

Surgical procedures of secondary importance were carried out during the afore-mentioned procedures when, in the opinion of the surgeon, such steps would enhance the subsequent result. Secondary procedures included appendectomy, uterine suspension, ovarian cystectomy, lysis of adhesions, and removal of endometriomas. Each operation was preceded by cervical dilatation and uterine curettage. Morbidity was noted postoperatively in 4 patients.

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Department of Case Reports New Instruments, Etc.

CORONARY OCCLUSION WITH MYOCARDIAL INFARCTION IN A PUERPERAL PATIENT

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CORONARY artery disease in women in the childbearing age is rare, and pregnancy following coronary occlusion is uncommon because pregnancy is usually avoided after this catastrophe.

Glendy,¹ in his series of 3,370 pregnant patients, found 1.5 per cent of these women under the age of 40 to have coronary artery disease. Vander Veer and Kuo² found that over an eleven-year period at Pennsylvania Hospital, 1.5 per cent of the pregnant patients treated had some form of heart disease. These figures correspond fairly well with the 1.7 per cent given by Hamilton,³ and the 1.8 per cent by Hamilton and Thomson,⁴ but were lower than the 2 to 3 per cent given by Stander,⁵ and Stromme and Kuder.⁶

Mendelson⁷ reviewed the literature in 1952 and found 21 cases of coronary artery disease in pregnancy and added 4 of his own. Of these 25 patients, 6, or 24 per cent died. Only 2 had autopsies. Early reports are not entirely reliable, however, or are inadequately reported, and many cases may not have been coronary disease. Klein⁸ cited only 3 authentic cases and added one of his own in March, 1953. In the same year, Brock⁹ reported on a myocardial infarction in pregnancy with a normal spontaneous delivery seven months later.

In Mendelson's⁷ review of 25 cases, there was only one patient, reported by Kolisko¹⁰ in 1916, who had a coronary thrombosis during the puerperium. The details were scant and there was no electrocardiogram, but she was reported as having died one month post partum of a thrombus of the descending branch of the left coronary artery as found at autopsy.

Case Report

A 28-year-old white primigravida was first seen on Feb. 21, 1953, at which time examination revealed an intrauterine pregnancy with the expected date of confinement on or about Sept. 22, 1953. The antepartum course was normal. She was a very tense, high-strung individual, hyperactive, and unable to relax.

The patient was admitted to the hospital on Sept. 30, 1953, in active labor. Progress was very slow in spite of strong contractions. She was given intravenous glucose solution and 0.015 mg. morphine sulfate at the end of eight hours. She relaxed somewhat, and when the contractions recurred in three hours, she began to make progress. This same procedure

was carried out later, the contractions causing good progress when they occurred. She was in the hospital approximately 27 hours before she delivered and slept about five or six hours of this time.

Delivery of the baby was carried out without difficulty with low outlet forceps and an episiotomy under Vinethene anesthesia.

The postpartum course was complicated by a severe headache which became much worse each time the patient raised her head from the pillow. Visitors were restricted from her room during this time because they seemed to contribute to her tension and to her headache. She was placed on Cafergot but this intensified the headache. Ergotrate and Cafergot were then stopped. By the sixth day she had improved considerably, and she was dismissed with sedation on the eighth postpartum day with a very mild headache, her general condition being good.

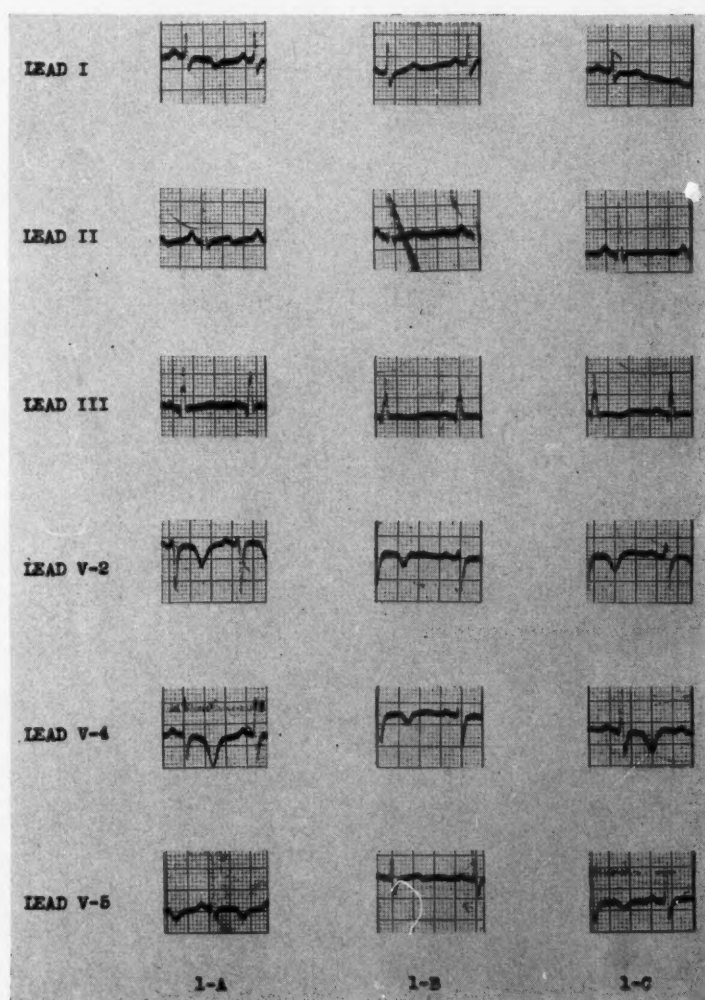


Fig. 1.—A, Inversion and coving of T-waves in Leads I, V-2, V-4, and V-5, with biphasic T-waves in Lead II; minimal R-wave in V-2. Acute coronary occlusion with myocardial infarction, anterior type.

B, Upright T-waves in Leads I and II, isoelectric in III; inverted T-waves in V-2 and V-4, biphasic in V-5.

C, Biphasic T-waves in Leads I and II; inverted T-waves in Leads III, V-2, V-4, and V-5 (recurrence of chest pain).

This patient did very well at home, was free of the headache, and had no complaints until the evening of Oct. 17, 1953, the seventeenth postpartum day. At that time she was watching television at her home with visitors when she was stricken with a sharp, severe pain in the left chest. She became extremely short of breath and very upset. The pain radiated from just left of the sternum to the left arm and down the ulnar side of the arm to the little finger. There was also some radiation from the chest to the tip of the scapula on the left side and a minor amount of pain in the right upper arm. She was readmitted to the hospital immediately.

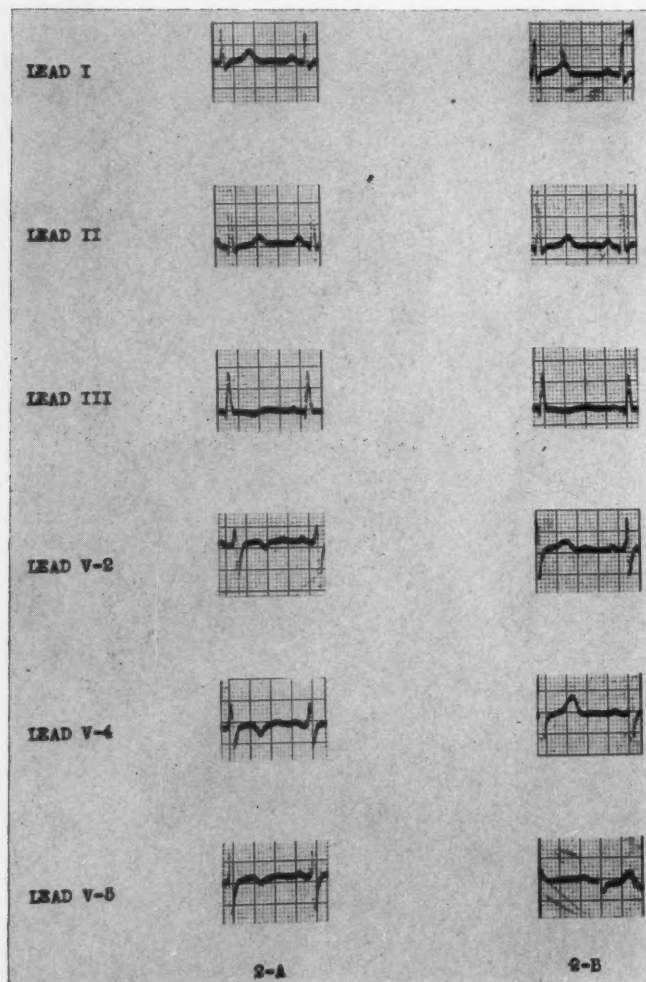


Fig. 2.—A, Upright T-waves in Leads I and II, slight inversion in III, inversion in V-2 and V-4, and biphasic T-waves in V-5.

B, Normal tracing with R-waves present in V-2 and T-waves upright in all Leads except III.

Examination disclosed a well-developed, well-nourished white woman, very pale, in acute distress with an anxious facies, severe shortness of breath, and cold, clammy skin. Her temperature was 98° F., pulse 80, respirations 20 (following Demerol), blood pressure 120/90. The remainder of the examination was normal for a patient in the puerperium. The impression at that time was: (1) possible angina pectoris; (2) an allergic reaction to derivatives of ergot; or (3) pulmonary embolism.

She was given 50 mg. Demerol and rested very well that night. There was no change in the blood pressure, pulse, temperature, or respiratory rate. The next day she was greatly improved. Two days after admission it was decided that an electrocardiogram should be done prior to dismissal in order to be sure that she had not had a coronary thrombosis even though her symptoms had been relieved by 50 mg. Demerol and had not recurred and even though her physical and laboratory findings were not indicative of myocardial infarction. This electrocardiogram showed a normal rate, rhythm, P-waves, and P-R interval. There were inversion and coving of the T-waves in Leads I, V-2, V-4, and V-5, with diphasic T-waves in Lead II. There was a minimal R-wave in V-2. Interpretation: Acute coronary occlusion with myocardial infarction, anterior type (Fig. 1, A).

She was placed on complete bed rest, sedation, and Dicumarol therapy. On Oct. 20, 1953, she developed an abscess of the right Bartholin gland which subsided within a week after treatment with hot compresses and antibiotics. A repeat electrocardiogram on Oct. 23, 1953, showed that the T-waves had become upright in Leads I and II, isoelectric in III. There was an inverted T-wave in V-2 and V-4, diphasic in V-5 (Fig. 1, B). One week later the electrocardiogram was again repeated, showing T-waves in Leads I and II to be diphasic, and to be inverted in Leads III, V-2, V-4, and V-5 (Fig. 1, C). At that time she had had a recurrence of pain in the chest. She improved and on Nov. 6, 1953, was dismissed from the hospital on Dicumarol therapy to be followed at home.

An electrocardiogram on Nov. 20, 1953, showed the T-waves to be upright in Leads I and II, slightly inverted in III, inverted in V-2 and V-4, and diphasic in V-5 (Fig. 2, A).

On Jan. 21, 1954, the electrocardiogram showed a normal tracing with R-waves present in V-2 and T-waves upright in all Leads except III (Fig. 2, B). She was taken off all medication and allowed to resume her normal activities. The latest tracing was taken on July 16, 1954, and was likewise normal in all respects. This patient has been seen several times since and is doing well.

Comment

This case is presented because so very few of this nature have been reported in the literature. A coronary occlusion in a young woman is quite unusual and its occurrence in the postpartum course is still more unusual. In a young, supposedly healthy individual, we do not often think of a coronary occlusion, but this case shows that they do occur. Some cases are probably not diagnosed in women who complain of indigestion, shoulder pain, chest pain, etc., and many times we pass them off too lightly. This patient might well have been given sedation in the home, have obtained relief from this, and a diagnosis of coronary occlusion never made.

This case shows the importance of a careful and complete consideration and investigation of all the symptoms of a pregnant patient, both before and after delivery, however trivial some of these symptoms might seem to be.

Summary

1. A case is presented of a primigravida who suffered a coronary occlusion on the seventeenth postpartum day, and who recovered completely under medical therapy.
2. A review of the available literature shows this to be a very rare occurrence.

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CEREBRAL HYPOXIA FROM AIR EMBOLUS FOLLOWING ATTEMPTED ABORTION

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ALTHOUGH sudden death has been reported following introduction of various foreign substances into the uterus, the number of women who have survived the manifestations of cerebral hypoxia following intrauterine administration of air is small. The following case is presented as an interesting addition to this select group.

Case Report

An unconscious 22-year-old gravida iii, para i, was brought to the emergency room on Jan. 17, 1953. Her husband stated that the patient consulted a physician two weeks before and was told she was three months pregnant. Though depressed in spirits, she seemed physically well until the evening of January 17 when, about one hour before she was first seen here, she went into the bathroom, inserted a rubber catheter into the vagina, and injected air through it with a bulb syringe. A few minutes later her husband found her lying unconscious on the bathroom floor. He said she appeared blue, and had trouble breathing. He brought her immediately to Parkland Hospital.

When first seen, she was cyanotic. Respirations were labored and stertorous. The blood pressure was 90/60; the pulse 80. The extremities were flaccid and all reflexes were absent. Frothy pink fluid bubbled from the mouth. There was bilateral strabismus. Since there was obvious obstruction of the airway, a tracheotomy was done and much pink frothy material was aspirated from the trachea. Breathing continued to be labored but cyanosis was relieved after this procedure.

The spinal fluid was clear, and its pressure was 140 mm. of water. The emergency room house officer drew blood for blood sugar determination, subsequently reported as 227 mg. per cent. The rectal temperature was 104° F., and later on in the evening of admission it rose to 107° F.

Two hours after admission, the patient passed a fetus and placenta of a size compatible with a three months' gestation. There was no significant uterine bleeding. Shortly thereafter, she began having generalized convulsions and made no conscious response to external stimulus. Convulsions recurred at intervals during the night, and next morning she demonstrated a stiff neck and spastic paralysis. The pupils were constricted, and the optic discs and cups, though difficult to visualize, appeared normal. At times, the eyes focused; at other times, they did not. Corneal reflexes were absent. Tendon reflexes were extremely hyperactive and equal. There was a bilateral Babinski sign. The patient now held both arms tightly flexed, but two days later the extremities again became flaccid. A neurological consultant concurred in the tentative diagnosis of severe cerebral hypoxia, possibly secondary to cardiac air embolism. A localized vascular occlusion seemed improbable because of evidences of involvement of both cerebrum and brain stem.

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The treatment regimen was purely supportive, comprised of parenteral feedings, antibiotics, meticulous nursing, maintenance of an adequate airway, and antipyretic measures. By January 22, five days after admission, there was gradual return of various body functions. On this day, the patient reacted markedly to painful stimulus, and constantly carried out swallowing motions. A polyethylene tube was maintained in the stomach, and a high caloric formula fed through it. The patient continued to be totally irrational. The respirations were no longer abnormal, however, and the tracheotomy tube was removed on January 27.

The patient then became disturbed and disturbing. At frequent intervals she cried out loudly, and seemed acutely distressed. Although she swallowed soft foods, she vigorously resisted attempts to touch her face or mouth. The eyes tended to deviate toward the right, but occasionally evidences of voluntary control appeared. The patient made continuous flexion movements of the head day and night, and she never seemed to be really asleep. Superficial and deep reflexes were now normal, and the Babinski sign had disappeared.

On the morning of January 31, two weeks after admission, there was sudden vaginal bleeding amounting to 150 c.c. Under Pentothal anesthesia, the uterus was found to be scarcely larger than normal, but the cervical os was greatly dilated, and contained a large fragment of placental tissue. This was removed, and a moderate quantity of placental tissue was curetted from the endometrial cavity.

The next day the patient showed, if possible, greater signs of distress than previously. A fecal impaction was removed with some quieting effect. Nevertheless, that night paraldehyde sedation was necessary to control her frightful screaming. Next day she was discharged to the care of her mother, who had proved herself competent to care for her. At the time of discharge, the patient showed the mental status of a small child, and was moody, petulant, and shifty. Her self-expression consisted chiefly of shrieking, but from time to time she would speak some monosyllable such as "Ma," "yes," or "Dad."

She was seen at intervals thereafter, and by May 8, 1953, nearly 16 weeks after induction of abortion, the amount of recovery was remarkable. The patient was rational, and talked sensibly. She exhibited good control of the arms, but walked with difficulty, demonstrating a reeling ataxic gait. On Sept. 13, 1953, there was some improvement in locomotion. She was able to carry out many household activities, and to care for her 3-year-old daughter with only slight help from her mother. In the intervening period, there has been almost complete recovery of all bodily functions.

Comment

This patient suffered cardiac air embolism following an attempt at self-abortion by intrauterine injection of air. She exhibited complete recovery from the resulting cerebral hypoxia syndrome. No record of a precisely analogous case was found, but parallel instances of central nervous system sequelae following attempted abortion by intrauterine injection of various substances have been reported often.¹⁻⁹

The classical pioneer experimental study of the effects of intravenous injection of air and other gases is that of Couty.¹⁰ Since that time, isolated observations have appeared at intervals, and the total number of reported cases of cardiac air embolism following attempts at abortion now numbers over a hundred. From these it appears that cardiac air embolism is usually fatal within a few minutes, presumably because the air bubble which is introduced into the venous system reaches the right side of the heart, where it impedes the cardiac pumping action by bringing about a sudden, extreme

augmentation of intraventricular pressure. This results in momentary fibrillation or standstill during which virtually no oxygenation is provided to the cerebral tissue. In the case reported here, the air bubble in question must have been small enough so that regular cardiac action was able to start again before the cerebral hypoxia reached the stage of irreversibility. The patient then passed through a stage of decerebrate rigidity, but recovered over a period of several months all but a few cerebellar functions. Of great, though incidental, interest was the fortuitously obtained blood sugar determination. It seems reasonable to interpret this marked elevation as an accidental parallel in the human of the *piqûre* experiments of Claude Bernard. The extreme hyperthermia in the absence of infection was presumably also hypothalamic in origin.

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MATERNAL DEATH DUE TO PULMONARY EMBOLISM OF TROPHOBLASTIC CELLS

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IT IS common knowledge that intrauterine trophoblastic cells, even in normal pregnancy, are transported to the lungs via vascular channels.² Under usual circumstances these emboli produce no symptoms and spontaneously disappear due to some local or systemic defense mechanism against trophoblastic cells as yet unknown.⁸ If a pulmonary embolus of trophoblastic cells is sudden and extensive enough, however, it could produce death. Dieckmann¹⁴ referred to such a case reported by Hughes and one by Mills, and Marcuse⁷ recently reported such a death in a woman with an estimated six months' pregnancy. The case here presented is one of sudden maternal death due to pulmonary embolism of trophoblastic cells from a benign intrauterine hydatidiform mole.

Case Report

A 19-year-old Latin-American woman, para 0, gravida ii, was admitted to the Fort Sill Army Hospital because of vaginal bleeding. She had been amenorrheic for three months. Vaginal spotting had occurred one week prior to admission and had continued intermittently since. On the day before admission she had experienced "cramps" and more profuse bleeding with some small clots.

Pertinent Physical Findings.—The patient was a well-developed woman not appearing ill. The blood pressure was 130/70, pulse 84. The fundus of the uterus was palpated four fingerbreadths above the umbilicus. Pelvic examination disclosed some blood in the vagina. The uterus was larger than the duration of gestation would indicate. The adnexa were negative without ovarian enlargement.

Laboratory Findings.—Analyses of catheterized urine specimens on the day of admission and the day of death were negative except for a trace of albumin in the latter. Blood studies on admission showed leukocytes 7,500, red blood count 3.3 million and hemoglobin 8.9 Gm. per 100 c.c. of blood. Several red count and hemoglobin determinations were done during the course in the hospital with the lowest determination of 5.6 Gm. on the thirteenth hospital day. She received 2,000 c.c. of whole blood by transfusion. Hemoglobin on the day previous to death was 10.8 Gm. per 100 c.c. blood with no significant bleeding thereafter. X-ray of the abdomen prior to death showed a uterus as large as a six months' gestation but no fetal bones were visualized.

The diagnosis on admission was threatened abortion. She had intermittent vaginal bleeding which was never profuse. She sporadically complained of "cramps" for which analgesics were given. Vomiting occurred occasionally. No fetal heartbeat or fetal parts were ever detected but on repeated occasions the patient stated she had felt fetal movement. Four days before death the patient developed a cough without sputum. The diagnosis of hydatidiform mole was considered but was never established as she had never passed any cysts or tissue per vaginam. A diagnosis of multiple pregnancy and hydramnios could not be excluded.

On the seventeenth hospital day, following visiting hours spent with her husband, the nurses' notes recorded that the patient seemed apprehensive, dyspneic, and slightly cyanotic. The blood pressure was 140/70. She was seen one hour later by a medical officer who found the respirations to be fast and grunting. The color was dusky to blue. The pulse was fast but regular. The pupils did not respond to light. A small amount of fresh blood was noted in the pharynx. The abdomen was soft. There was no vaginal hemorrhage. Reflexes were present but diminished. The patient was given oxygen and Coramine but during the next 25 minutes respirations and pulse ceased. The impression at the time of death was "possible massive pulmonary embolus."

Fig. 1.

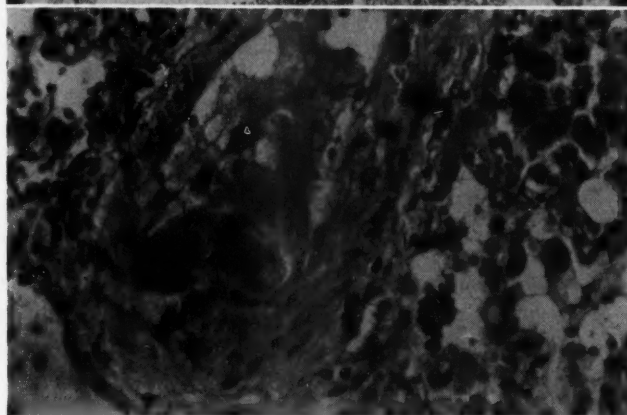
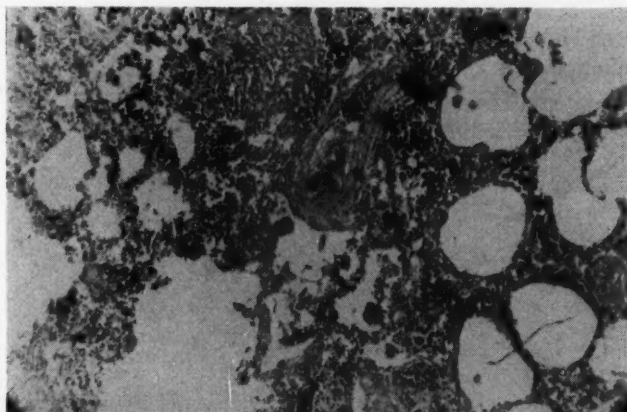


Fig. 2.

Fig. 1.—Section of lung periphery with parenchymal changes about an obliterated vessel ($\times 64$).

Fig. 2.—Higher magnification of Fig. 1 showing the trophoblastic embolus within the vessel lumen ($\times 280$).

Autopsy Findings.—

Gross: The uterus measured 27 cm. above the symphysis and was a bluish-gray color, soft and very pliable. The uterus with adnexa weighed 2,220 Gm., and measured 18 cm. in width and up to 16 cm. in thickness. It was thin walled and the cavity was filled with a large amount of grayish-tan, friable tissue. Clusters of cystic structures measuring up to 2 cm. in diameter were scattered throughout the intrauterine tissue. The cysts contained clear, watery fluid. In the lower portion of the uterus, forming a barrier between the hydatidiform mole and the cervix, was a large amount of laminated and organized-appearing blood clot, the volume of which was estimated to be approximately 700 c.c. The ovaries averaged 5 by 4

by 3 cm. and on sectioning revealed numerous small cystic spaces measuring up to 2 cm. in diameter that were filled with clear, watery fluid and lined with fairly smooth membranes.

The right side of the heart was somewhat dilated and filled with blood and the pulmonary conus broadened. The left ventricle was in systole and there was a slight clockwise rotation of the heart along its long axis. The right lung weighed 730 grams, the left 710 grams. The cut surface of the lungs were markedly congested and small patchy areas of lighter-appearing parenchyma were scattered throughout. Crepitation was diminished throughout. The blood vessels contained no grossly demonstrable emboli.

Microscopic: The positive findings were mainly confined to the lungs. Scattered throughout were patchy areas of infarction with hyaline membrane formation. Between the infarctions were zones of normal-appearing alveoli. The most striking feature of the lungs was that the smaller blood vessels, 1 mm. in diameter or less, especially near the periphery of the lung, were filled with syncytial giant-cell masses (Figs. 1, 2). The larger blood vessels were free of embolic material. Weigert's stain for fibrin showed no fibrin thrombi in the smaller vessels of the lung or in those of the kidney or adrenal. Brain sections showed syncytial cell masses in the pia arachnoid vessels and some hyaline thrombi in the cerebellar vessels. One such thrombus studied under oil showed the presence of fibrin, erythrocytes, and a single epithelioid cell. Focal myocarditis, probably from hyaline thrombi, was present and minimal.

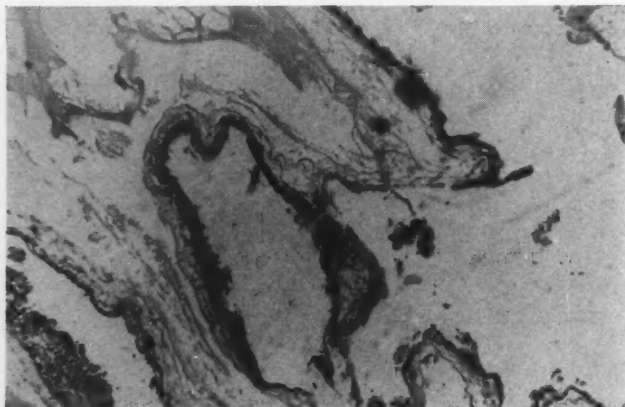


Fig. 3.—Section of hydatidiform mole with central villous cystic degeneration and trophoblastic hyperplasia ($\times 85$).

The hydatidiform mole within the uterus showed typical cystic degeneration of the central core of the chorionic villi with proliferation of the trophoblasts (Fig. 3). The trophoblasts were slightly hyperchromatic and there was some vacuolization of the nuclei but the change was not extensive enough to indicate malignant degeneration and it was classified as Hertig's Type II. A single sinusoidal vessel of the uterus contained a thrombus of hyaline and syncytial cells. The ovaries contained numerous small follicular cysts and many large lutein cysts.

Comment

Physiologically normal trophoblast has characteristics of malignancy, namely, destructive invasion of tissue and permeation of blood vessels.⁸ A characteristic of hydatidiform mole and an essential for its pathological diagnosis is accentuated trophoblastic proliferation. Furthermore, this trophoblastic proliferation is greatest on or in the myometrium where the blood supply is best.⁸ Therefore, that molar trophoblasts frequently invade the myometrium and have been found in maternal myometrial blood spaces is

easily comprehended. Hemoptysis, x-ray densities of the lungs, and post-mortem microscopic proof of pulmonary trophoblast have been reported^{8, 10} in benign hydatidiform mole. Potentially then, in this patient, the source of the trophoblastic emboli was the benign intrauterine hydatidiform mole. The finding of trophoblastic cells in a maternal uterine sinusoid tends to substantiate this assumption. Whether any incident (uterine trauma, contraction, etc.) set forth the terminal embolism to produce death of this patient remains unknown.

Experimentally and clinically, two types of pulmonary embolism are recognized^{3, 4}: (1) syncopal embolism due to occlusion of the pulmonary artery or its main branches (vascular thrombi) characterized by pallor, lowered blood pressure, and normal oxygen saturation of peripheral arterial blood, and (2) asphyctic embolism due to occlusion of the peripheral vascular bed of the lung (fat, air, amniotic fluid), characterized by cyanosis, dyspnea, lowered oxygen saturation of the peripheral arterial blood, and a maintained or slightly lowered systemic blood pressure.

From animal experiments approximately 60 per cent of the pulmonary artery must be occluded (syncopal embolism) before severe to fatal signs begin to appear. In contrast, occlusion of the peripheral pulmonary arterial and capillary beds (asphyctic embolism) produces profound symptoms and death with a considerably smaller percentage of occlusion. No one experimentally or clinically has estimated the amount of peripheral vascular occlusion to be fatal but in many cases it has been small.^{5, 6, 12} In asphyctic embolism additive factors, over mere mechanical occlusion of the vessels, are thought to accentuate the process. Suggested additive factors have been: reflex spasm of collateral arterioles, reflex vagal depression of the heart,³ resultant pulmonary edema, resultant thrombi of inflammatory cells, anaphylactoid reaction,^{1, 5, 6, 12} and, in cellular emboli, release of histamine⁵ and resultant intravascular fibrin thromboembolism. Irrespective of the exact mechanisms involved, circulation through the pulmonary vascular bed is decreased. The heart initially may compensate for the increased peripheral resistance in the pulmonary circulation by increased force of contraction but eventually if the occlusion is progressive and with resultant relative anoxia of the heart, more blood enters than leaves the right heart producing dilatation, designated as acute cor pulmonale. Whether death is due to anoxia or heart failure is irrelevant.

In the contemplation of pulmonary embolism as the cause of death in this case, the physiological death is largely explained by anatomical methods. We believe that the signs of cyanosis and dyspnea with an essentially normal blood pressure suggest asphyctic embolism. The post-mortem findings of trophoblastic emboli in the smaller vessels of the lungs, pulmonary edema, and right heart dilatation establish pulmonary embolism of trophoblastic cells as the immediate cause of death. We further believe that

this patient had trophoblastic emboli previous to her terminal episode as manifested by infarcts in the lungs but that the last "shower" of emboli exceeded her physiological tolerance of pulmonary embolism.

The concept that intrauterine hydatidiform mole invades the myometrium and its blood spaces suggests a pertinent clinical aspect of this problem. Trauma incident to examination, dilatation and curettage, or hysterotomy in advanced hydatidiform mole might reproduce the case herein described.

Summary

1. A case of hydatidiform mole (Hertig's Type II) is presented.
2. Maternal death was caused by pulmonary emboli of trophoblastic cells from the intrauterine hydatidiform mole.

Addendum.—The finding that placental tissue is rich in thromboplastin suggests that sublethal cases similar to the one described, in so far as pulmonary embolism is concerned, might subsequently be fatal by the production of intravascular fibrin thromboembolism^{9, 11} and resultant hypofibrinogenemia. There is the possibility that some of the deaths in hydatidiform mole attributed to "shock" and "hemorrhage" might be due to pulmonary emboli of trophoblastic cells, fibrin thromboembolism, and hypofibrinogenemia. The suggestion is made that in cases of hydatidiform mole with severe hemorrhage blood studies be made for fibrinogen, plasma thrombin inhibitory activity, platelets, and plasma fibrinolysins,^{9, 11, 13} and that in fatal cases the lungs be studied histologically for trophoblastic and fibrin thrombi.

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EXTENSIVE CEREBRAL HEMORRHAGE CAUSED BY THE RUPTURE OF A CEREBRAL BLOOD VESSEL DUE TO A CHORIONEPITHELIOMA EMBOLUS

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THE following case of chorionepithelioma is reported because of certain interesting points some of which are controversial and will be discussed after the history is presented.

M. D., a 40-year-old gravida vii, para vi, was admitted to the Philippine General Hospital on March 30, 1954, with the complaint of a painful mass in the hypogastrium which had been noticed two weeks previously.

In the latter part of August, 1953, she was curetted for hydatidiform mole in a provincial hospital. She was amenorrheic during September and October and on November 16 she had abdominal pains accompanied by the passage of blood clots and whitish material interpreted by a private physician as an abortion of two months. Thereafter, she continued to pass pale bloody discharge for which she was again curetted in the same provincial hospital on Jan. 16, 1954. The bleeding stopped and she was discharged after 8 days' stay in the hospital. In February, 1954, or one month after the second curettage, she had pinkish vaginal discharge for 2 days. In March she had no bleeding, but she noticed a globular, nontender mass which increased rapidly in size. It was for this abdominal mass that she consulted the dispensary of the Philippine General Hospital, where the diagnosis of ovarian cyst was made and she was recommended for admission to the hospital.

On admission, she was pale, with a temperature of 37.5° C.; pulse 92; respiration 24; blood pressure 164/78 mm. Hg; red blood count 3.25 million; white blood count 6,800. The frog test for both urine and spinal fluid was positive. X-ray of the chest showed in each lung one 10 cent sized shadow of metastasis. Abdominal examination showed the uterus to be globular, soft, cystic, and enlarged to the size of a 4 months' pregnancy. On internal examination, the left labium majus had an oval nontender cyst, 2 mm. in diameter. The cervix was small, soft, and closed. Above the right fornix corresponding to the right parametrium was felt an orange-sized firm mass closely connected with the lower segment of the uterus.

Because of the history of passage of mole, bleeding, enlargement and softening of the uterus, the positive hormonal test, and the shadows in the lungs, the diagnosis given was uterine chorionic malignancy with pulmonary metastasis.

Under spinal anesthesia a laparotomy was performed. Total hysterectomy, bilateral salpingo-oophorectomy, excision of the orange-sized parametrial growth together with its contained ureter, and implantation of the right ureter into the sigmoid were done.

Sagittal section of the 4 month sized, soft, boggy uterus showed a distended uterine cavity filled with whitish, cheesy, slimy, necrotic material wherein were discerned a few 1 mm. sized cystic structures with thick, opaque walls. The orange-sized metastatic growth in the right parametrium, in contrast to the degenerated contents of the uterine cavity, was a firm hemorrhagic solid tumor biopsy of which showed chorionepithelioma.

On the day following the operation, the patient complained of slight headache which was alleviated later. The headache was attributed to the spinal anesthesia. During the first three days she complained of postoperative pain, and the temperature reached 38.9° C.

On the third day, the temperature fell to normal. There was slight vaginal bleeding and slight headache. On the fifth day, she felt well and began to walk. She continued to feel well and never complained of cough or chest oppression, but in the afternoon of the ninth day, she complained of severe headache and at 4:00 o'clock the following morning she was found dead by the nurse.

Autopsy.—

Abdominal cavity: Except for the flimsy adhesions of the omentum to the anterior abdominal peritoneum, the absence of the uterus and adnexa, and the presence of the implanted ureter in the sigmoid, no abnormality was found.

Microscopically, the endometrium and myometrium of the removed uterus as well as the orange-sized parametrial growth also removed at operation showed clusters of Langhans cells some of which were found inside the veins. There were few syncytial cells.

In the vagina near the introitus was a hematoma surrounded by clusters of malignant cells.

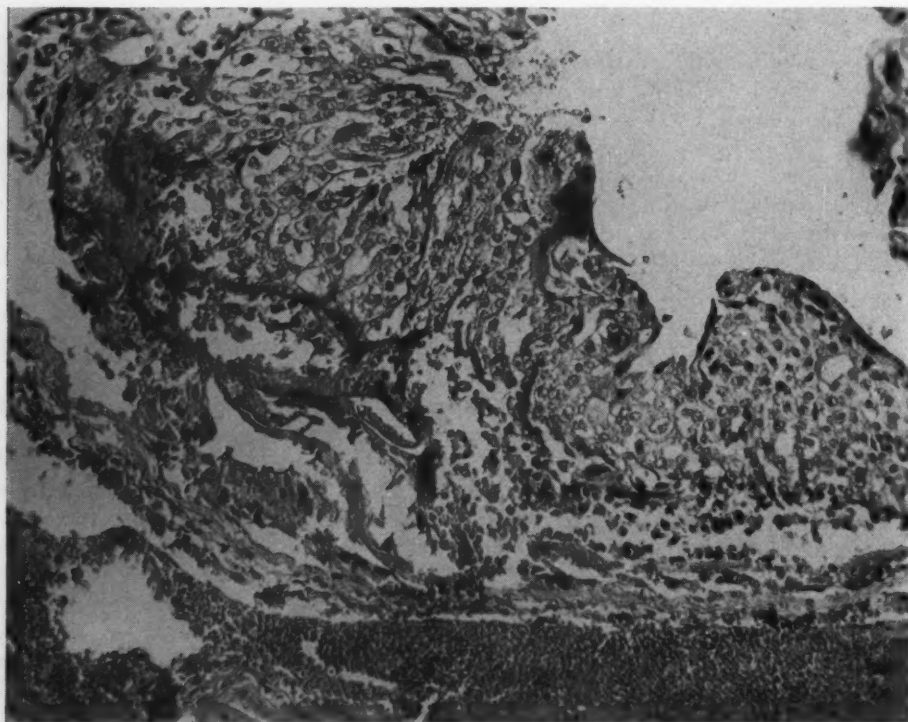


Fig. 1.—Cerebral blood vessel within which is an embolus of Langhans and syncytial cells.

Lungs: Both lungs showed red patches on the surface, and on section multiple hemorrhagic granular circumscribed nodules from a few millimeters to 1.5 cm. in diameter. Microscopically, the nodules showed clusters of malignant Langhans cells surrounded by large areas of hemorrhage. Some of the clusters were seen invading the blood-vessel walls, and some were found in the lumen.

Brain: There was a massive subdural hematoma covering the whole right cerebral hemisphere. The brain was found to be ruptured at the right parietal region, and at the site of rupture was a big clot of blood. On microscopic section no malignant cells were seen in the brain substance but at the site of rupture there was an artery containing an embolus of malignant Langhans cells. There was destruction of the arterial wall giving rise to extensive bleeding. Around the hemorrhagic area were polymorphonuclear leukocytes and lymphocytes (Fig. 1).

Comment

With the diagnosis of chorionepithelioma, I believe there will be no disagreement. It is supported by the microscopic findings, there were metastases, the patient died.

But what is controversial is the source of the chorionepithelioma cells. Is it from the hydatidiform mole curetted by an outside physician 7 months before admission to the Philippine General Hospital, or is it from an abortion of 2 months which was supposed to have been completed by the same physician 2½ months before she was admitted to the Philippine General Hospital?

Abortion is indeed one of the precedents of chorionepithelioma, especially if it is an early one of 2 months. It is also possible that after curettage for hydatidiform mole the patient may immediately become pregnant, though usually this does not occur. The diagnosis of abortion of a 2 months' pregnancy following mole in this case apparently was based on the 2 months' amenorrhea following the curettage for mole and the expulsion of blood clots and whitish material thereafter. No fetus could be identified, though the absence of the fetus does not rule out abortion.

It is possible that such a sequence occurred. However, I do not believe this patient had a new pregnancy after the expulsion of the mole for the following reason.

When the patient was admitted to the Philippine General Hospital, which was 2½ months after she was curetted for the completion of the supposed abortion at 2 months, the size of the uterus was that of a 4 months' pregnancy and, on sagittal section, the distended uterine cavity was filled with whitish, cheesy, slimy, necrotic material which apparently was remnants of degenerated minute hydatidiform mole cysts. It was this abundant necrotic material that gave the uterus its very soft consistency, which made the physician in the dispensary diagnose the case as ovarian cyst.

I do not believe that the whole amount of the necrotic material in the uterus developed in 2½ months. What was interpreted as fetal structure must have been part of this whitish material which became more necrotic later. All the whitish necrotic substance was confined in the uterine cavity.

In the region of the right parametrium, however, closely connected with the isthmus uteri, was an orange-sized hemorrhagic solid mass which grossly and microscopically showed the characteristics of chorionepithelioma. The growth, in contradistinction to the uterine content of degenerated material, looked like an active tissue and of more recent development and seemed to be the source of metastasis in other parts of the body.

This is one of the eight cases of uterine chorionepithelioma that has been observed by the author to show amenorrhea of one to three months after the expulsion of the product of conception (which gave rise to malignancy), before the occurrence of abnormal bleeding.

Grateful acknowledgment is made to Drs. P. Cruz and Antonio R. Lahoz of the Pathology Department for the autopsy data and their interpretation, and also for the illustration here presented.

SILENT, ASYMPTOMATIC RUPTURE OF THE UTERUS FOLLOWING NORMAL LABOR AND DELIVERY*

With Two Case Reports

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THE diagnostic term "rupture of the uterus" is used to denote perforation from any cause after fetal viability has been established. This accident may occur once in 3,000 deliveries, and accounts for 5 per cent of the maternal deaths in the United States. It may occur before or during labor.

Many predisposing factors have been recognized and implicated in rupture of the uterus. These could be summarized as follows: multiparity, previous cesarean section, disproportion, abnormal presentation, uterine abnormalities of many types (congenital, previous uterine infection, placental erosion, and tumors), obstruction in the birth canal, and chronic nutritional deficiencies. In addition, more dynamic or precipitating causes have been cited, such as manipulative delivery, use of oxytocic drugs, severe and prolonged labor, and trauma. Rupture of the uterus usually produces the classic picture of severe abdominal pain, marked symptoms of collapse, cessation of uterine contractions, and usually some external bleeding.

The type of uterine rupture discussed here produced no symptoms and was unsuspected. It was silent in nature, associated with normal labor, and not connected with any traumatic procedure.

CASE 1.—Mrs. E. L. C., a gravida vii, para iv, aged 27 years, was admitted for the first time on March 10, 1952, at 5:30 A.M., having mild irregular uterine contractions. Her pregnancy had been uneventful except for slight vaginal bleeding during the second month for two days. The estimated date of confinement was March 6, 1952. Physical examination on admission was completely normal. Rectal examination on admission disclosed a minus 3 station with no dilatation of the cervix. The patient was given a saline enema. Contractions ceased and she was discharged at 1:30 P.M. with a diagnosis of false labor. Her previous obstetrical record is given in Table I.

TABLE I. PREVIOUS PREGNANCY RECORD OF E.L.C.

| DATE | LENGTH OF LABOR | TYPE OF DELIVERY | WEIGHT OF BABY | REMARKS |
|------|--------------------|------------------------------------|--------------------|------------------|
| 1944 | 48 hours | Low forceps, episiotomy | 6 pounds, 3 ounces | Inertia |
| 1945 | 6 hours | Low forceps, episiotomy | 6 pounds, 4 ounces | No complications |
| 1946 | | Spontaneous abortion at two months | | No complications |
| 1948 | 12 hours | Spontaneous delivery | 7 pounds, 4 ounces | No complications |
| 1949 | 4 hours | Spontaneous delivery | 6 pounds, 4 ounces | No complications |
| 1950 | | Spontaneous abortion at six weeks | | No complications |

*Presented at the Quadri-city Dallas-Ft. Worth Obstetrical and Gynecological Society, Dallas, Texas, April 30, 1955.

The patient was readmitted on March 11, 1952, at 8:30 P.M. in early labor. The blood pressure was recorded as 120/56, pulse, 96, and respirations 18. The fetal heart tones were 160 in the left lower quadrant. Rectal examination showed a vertex presentation at station minus 1, and the cervix was dilated 3 cm. Contractions were moderate in intensity. At 9:45 P.M., the contractions were occurring every 4 minutes and lasting 45 to 50 seconds. Rectal examination showed a station of zero with 4 cm. dilatation. The patient was given 100 mg. of Demerol and 1/150 grain of hyoscine intramuscularly. She was also given 3 grains of Seconal orally. The blood pressure at this time was 118/70 and pulse 70. At 11:18 P.M. the cervix was completely dilated and she was taken to the delivery room. Fetal heart tones were 150 in the left lower quadrant. At 11:20 P.M. under gas analgesia, she had a spontaneous delivery of a normal male infant weighing 6 pounds, 2 ounces, with no episiotomy or laceration. The placenta was delivered spontaneously and intact at 11:27 P.M. Blood loss was recorded as minimal. The patient was given 1/320 grain Ergotrate intravenously at the completion of the third stage.

On admission to the postpartum floor at 11:40 P.M., the fundus was firm and there was no excessive vaginal bleeding. The blood pressure was recorded at this time as 114/74, pulse 88, and respirations 20. The patient spent an uneventful night with no excessive vaginal bleeding. The hemoglobin was recorded as 11 Gm. per 100 ml. of blood after delivery.

The patient had no complaints on the morning of March 12, 1952, except for some "gas pains." She had received no medication for pain during this interval.

At 9:00 A.M. of March 12, 1952, she was prepared for tubal ligation. The blood pressure was recorded as 100/80, pulse 76, and respiration 16 at the beginning of anesthesia.

The abdomen was entered through a short midline subumbilical incision. It was noted that the peritoneum was blue. Approximately 500 c.c. of liquid and clotted blood was found in the peritoneal cavity. Inspection of the uterus disclosed a rent 5 cm. in length in the posterior wall at the junction of the corpus and cervix, extending through the serosa and muscle and out to the uterine vessels, but which did not go through the endometrium. A subtotal hysterectomy was performed without incident. The patient's blood pressure and pulse remained stable throughout the procedure and was 120/80 and 100 respectively at the end of surgery. She received 500 c.c. of whole blood during the operation.

The patient was placed on antibiotics and Wangensteen suction postoperatively. The hemoglobin on March 13, 1952, was recorded as 8.2 Gm. per 100 ml. and she was given another 500 c.c. of whole blood. Her highest temperature was recorded as 101.8° F. on March 14, 1952, and on March 15, 1952, she became afebrile. The hemoglobin on that date was 10.2 Gm. per 100 ml. She was discharged in good condition on March 18, 1952.

CASE 2.—Mrs. K. F. C., a gravida iv, para iii, aged 36 years, was admitted in early labor on Jan. 14, 1953, at 2:00 P.M. Physical examination on admission was completely normal with a blood pressure of 122/70, pulse 86, and respirations 18. The pregnancy was at term with a vertex presentation and fetal heart tones of 140 in the left lower quadrant. The initial rectal examination showed an effaced cervix with 1 cm. dilation, the head at minus 1 station and the membranes intact. Her previous obstetrical history is given in Table II.

TABLE II. PREVIOUS PREGNANCY RECORD OF K.F.C.

| DATE | LENGTH OF LABOR | TYPE OF DELIVERY | WEIGHT OF BABY | REMARKS |
|------|-----------------|-------------------------|--------------------|------------------|
| 1937 | 13 hours | Low forceps, episiotomy | 8 pounds, 7 ounces | No complications |
| 1945 | 10 hours | Low forceps, episiotomy | 7 pounds, 7 ounces | No complications |
| 1947 | ½ hour | Spontaneous delivery | 7 pounds, 8 ounces | No complications |

Her labor progressed slowly with moderate contractions every 4 to 5 minutes. At 5 P.M., rectal examination showed a station zero with 3 cm. dilatation. At 9:25 P.M., contractions were stronger, lasting 50 seconds and occurring every 4 minutes. The patient was given Demerol, 100 mg., and scopolamine, 1/130 grain intramuscularly. At 11:00 P.M., Demerol,

50 mg., was given intramuscularly. At 12:01 A.M., Jan. 15, 1953, rectal examination showed a dilation of 5 cm. with a station zero, and $\frac{1}{300}$ grain of hyoscine was given intramuscularly. At 1:30 A.M., the cervix was completely dilated with a station plus 1. The blood pressure was recorded as 110/70, pulse 86, and fetal heart tones 140 in the left lower quadrant. At 1:54 A.M., the patient was delivered spontaneously under gas analgesia of a 7 pound live female infant. The placenta was expressed intact with mild fundal pressure at 1:58 A.M., and the patient was given Ergotrate, $\frac{1}{320}$ grain intravenously. Blood loss during delivery was less than 100 c.c.

On admission to her postpartum room at 2:30 A.M., the fundus was firm and no excessive vaginal bleeding was noted. At this time, the blood pressure was recorded as 120/80, with a pulse of 74 and respirations of 18.

At 7:00 A.M., her temperature was 100.4° F. pulse 94, and respirations 20. The patient had no complaints. Her temperature was normal on two other occasions during this day and her pulse was recorded from 70 to 80 with respirations of 18.

On the morning of Jan. 16, 1953, the temperature was 98° F., pulse 70, and respirations 18. The hemoglobin was recorded as 12.8 Gm. per 100 ml. The patient had no complaints and had received no medication for pain since delivery. At 2:10 P.M., she was prepared for tubal ligation. The blood pressure was 120/80, pulse 82, and respirations 18 at the start of anesthesia.

The abdomen was entered through a subumbilical incision, and approximately 100 c.c. of free blood was found in the abdominal cavity. Examination of the uterus showed a tear in its anterior surface near the fundus running diagonally from right to left, approximately 5 cm. in length and 2 cm. in depth. The tear involved the serosa and musculature of the uterus, but did not extend through the endometrium. There was no bleeding at the time of operation. The laceration was sutured with interrupted chromic No. 0 catgut sutures. The tubes were then visualized and a Pomeroy type of tubal ligation was performed. The abdomen was then closed in layers.

The patient's postoperative convalescence was completely uneventful and she was discharged on January 19 in good condition.

Comment

Neither of these cases presented any of the classical signs or symptoms of uterine rupture. Each patient experienced a normal labor, an atraumatic delivery, and a normal postpartum course. Neither patient complained of any pain following delivery, nor did either show any sign of intra-abdominal hemorrhage. The previous deliveries of both had been without complication.

The diagnosis of uterine rupture under these circumstances cannot be made except by laparotomy for other indications. These cases are presented as a possible explanation for a classical rupture of the uterus in subsequent pregnancies. It is impossible to estimate how often such an asymptomatic, partial rupture of the uterus may occur. Routine intrauterine exploration will not confirm this type of rupture, as in both cases the tear involved only the peritoneal covering and the muscle of the uterus, with an intact endometrium. This type of rupture cannot be classified under the usual terminology. According to Stander: "It is customary to distinguish between complete and incomplete rupture, according as the laceration communicates directly with the abdominal cavity, or is separated from it by the peritoneal covering of the uterus or the broad ligament."

Summary

1. Attention is drawn to a group of uterine ruptures occurring during labor that are silent and asymptomatic; they are not associated with any of the classical signs.

2. Two case histories are presented. Both cases were diagnosed by incidental laparotomy for postpartum tubal ligation for other indications.

3. This type of partial rupture of the uterus cannot be classified under the usual terminology.

4. These cases are presented as a possible explanation for complete rupture of the uterus following normal labor in subsequent pregnancies.

We wish to thank Drs. W. K. Strother and S. Alexander for the use of their cases in the preparation of this paper.

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3702 WORTH STREET

PLACENTAL POLYPS—AN UNUSUAL CAUSE OF POSTMENOPAUSAL BLEEDING

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ALTHOUGH pregnancy has occasionally been reported after the complete cessation of menstruation, a review of the recent literature on placental polyps¹⁻⁷ does not refer to the occurrence of this clinically rare postgestational complication after the menopause. The following case of placental polyps, occurring five years after the menopause, is presented as an unusual cause of postmenopausal bleeding.

Case Report

M. G. (Mercy Hospital No. 76323), a 57-year-old white nulliparous secretary, was admitted Sept. 13, 1954, with a history of painless bright red vaginal bleeding, of minimal extent, for ten days. She had noted no other vaginal bleeding or leukorrhea since her menopause, five years previously. Her menopause was characterized by progressive hypomenorrhea. She had been separated from her husband, and denied sexual contact, during the four years prior to admission. The patient had never been pregnant to her knowledge; nor had she ever experienced any of the usual gestational signs or symptoms.

Physical examination on admission disclosed the following pertinent findings: (1) the blood pressure was 190/100; and (2) a friable, easily bleeding bluish-red polyp, approximately 1.5 cm. in diameter, protruded from the external os of the well-epithelized cervix. The uterine fundus was anterior and of normal size, shape, and consistency. The cervical Papanicolaou smear was Class III. A preoperative diagnosis of endometrial polyp was made.

On Sept. 15, 1954, under intravenous Surital anesthesia, dilatation and curettage and cervical biopsies were done. The tissue previously seen at the external os was no longer present; the patient had experienced no increase in the quantity of vaginal bleeding, nor low abdominal cramps, prior to operation. Curettage was productive of four distinctly separate necrotic-appearing polypoid structures varying from 0.5 to 2.0 cm. in diameter. It was the operator's impression that these polyps had their origin each from a different segment of the uterine cavity. In addition, a small amount of grossly normal-appearing endometrium was obtained.

Microscopic examination showed thickening of the squamous epithelium of the cervix and chronic cervicitis. The endometrial glands were large; some of these were tortuous and lined by a single layer of columnar epithelium, while others were lined by a stratified columnar epithelium. The endometrial stroma contained many large vessels, some of which contained antemortem thrombi; in some areas, a decidual reaction of pregnancy was noted (Figs. 1 and 2). Sections of the four polypoid structures showed considerable necrosis with persistence of the oval and circular outlines of degenerated chorionic villi (Fig. 3). No evidence of malignancy was noted.

Postoperatively the patient did well. She was discharged on the second postoperative day. One month later she was asymptomatic, and the pelvic findings were negative. The Papanicolaou smear reverted to Class II.

Fig. 1.

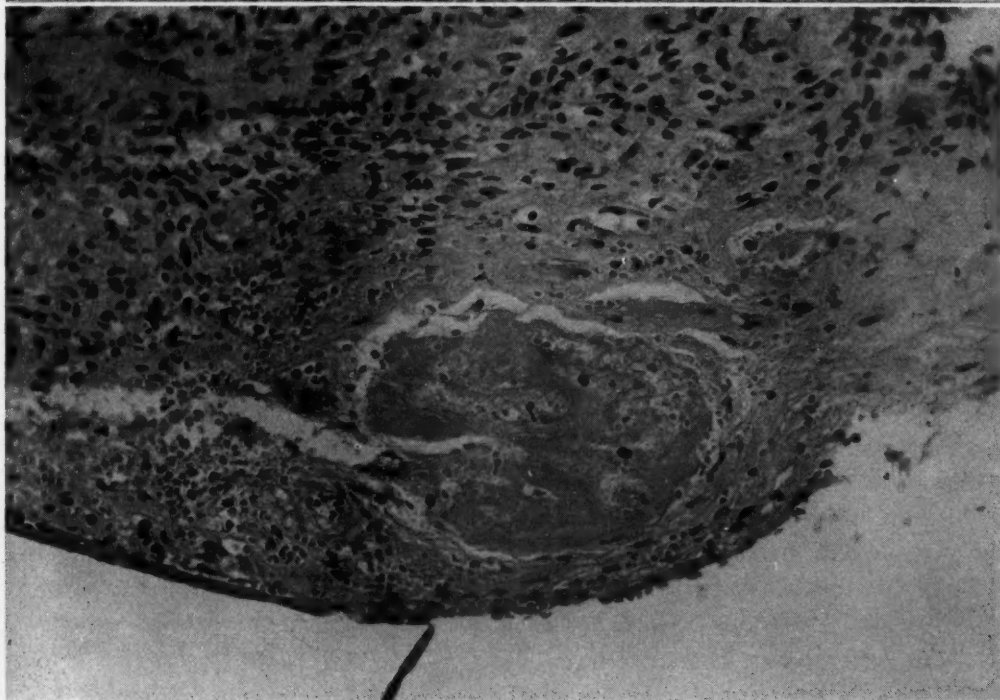
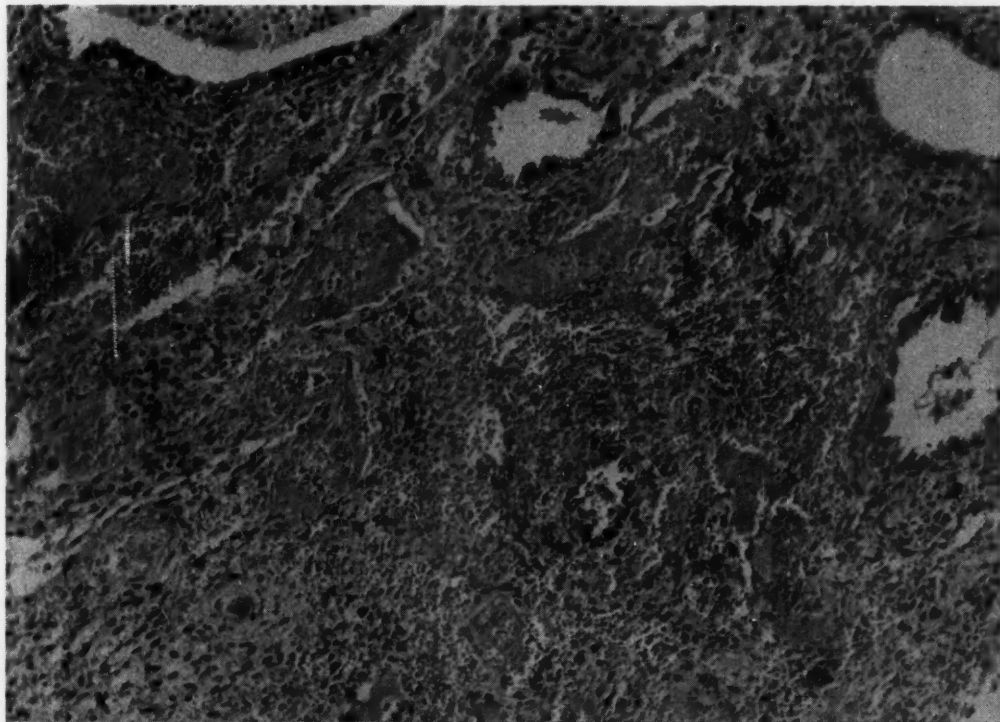


Fig. 2.

Fig. 1.—Near the base of one of the placental polyps. The typically vascular and hemorrhagic stroma contains many large intra- and extravascular antemortem thrombi. Upper central portion demonstrates old degenerated decidua. ($\times 150$; reduced $\frac{1}{4}$.)

Fig. 2.—A section from the edge of one of the placental polyps. Above the thrombus note the degenerated decidua. ($\times 240$; reduced $\frac{1}{4}$.)

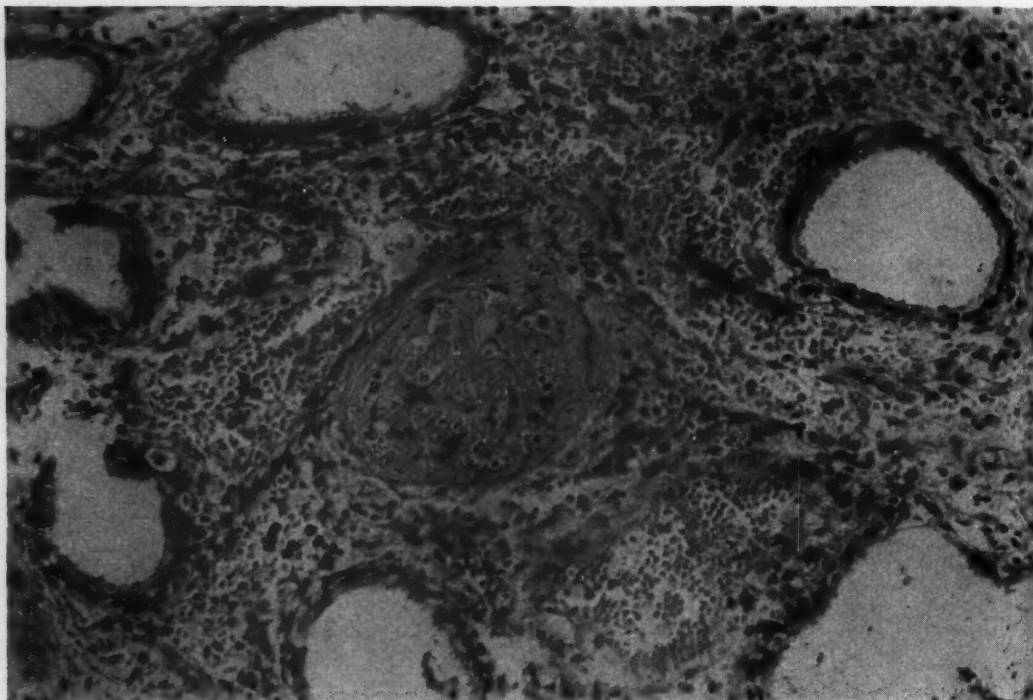


Fig. 3.—Near center, note one of several structures representing a degenerated chorionic villus with disappearance of the trophoblastic layers. The endometrial glands, while large, do not appear actively hyperplastic. (X240; reduced $\frac{1}{4}$.)

Comment

Curtis⁵ designated placental polyps as "portions of placental tissue of varying size which may be retained within the uterus for an indefinite period after abortion or full-term pregnancy." Rock¹ stated that placental polyps are formed by slow bleeding from around a fragment of attached chorion into, or onto, an already partially organizing blood clot. These polyps may protrude from the external os of the cervix so as to resemble a prolapsed endometrial polyp. It is known that the surface of a placental polyp may become necrotic enough to cause excessive vaginal bleeding, especially prior to its spontaneous expulsion, when the necrosis may extend into a large venous sinus at the base of the polyp. Spontaneous expulsion is not always associated with excessive bleeding, however, as in this case, in which no increase in vaginal bleeding was reported preoperatively. It is probable that one of the polyps had become detached several days prior to admission, and was then spontaneously expelled prior to operation as any foreign body or non-viable tissue lying unattached in the endocervical canal might be.

This patient was known to have had hypertension for thirteen years. One might speculate what role the associated long-standing vascular changes may have played in the bleeding from, and separation of, one of the placental polyps in her case. Ries³ reported placental villi in the uterine vessels eighteen years after the last delivery. Perhaps the placental polyps in this case might

have caused symptoms even later in the postmenopausal period, with or without persistent hypertension. Absorption of the polyps would have been another theoretically possible course of events.

Careful and thorough microscopic examination of all the curetted tissue was made to rule out coexisting malignancy. The possibility of a chorion-epithelioma arising within a placental polyp should always be considered.

Summary

1. A case of placental polyps occurring five years after the menopause is reported.
2. This condition represents an unusual cause of postmenopausal bleeding.
3. A symptomatic placental polyp, occurring one or more years after the last pregnancy or abortion remains a clinical rarity.
4. Expulsion of a placental polyp is not always associated with profuse vaginal bleeding.

The author wishes to express his appreciation to Dr. Gerald C. Leary for his interpretation of the photomicrographs.

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SPONTANEOUS FIBROID ENUCLEATION CAUSING POSTPARTUM INTRAPERITONEAL HEMORRHAGE*

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INTRAPERITONEAL hemorrhage from fibromyomas has been reported in approximately 50 cases.^{1, 2} The cause of the bleeding usually given is rupture or erosion of the wall of a vein.^{2, 3, 4} Eastman⁵ states, "It should be remembered that completion of labor does not necessarily indicate that all danger is past since the tumor may undergo gangrenous changes during the puerperium." Hodgkinson and Christensen⁴ in their excellent review of uteroovarian vein rupture in 1950 mentioned 72 cases and added 3 of their own. In none of these cases was a tearing of the serosa and outer muscularis of the postpartum uterus the source of the bleeding.

Case Report

Mrs. B. V., aged 42 years, gravida v, para iii, entered St. James Hospital at 3:00 P.M. on March 18, 1954, in early labor. She was at term but did have a somewhat unusual past history. She had been operated upon one year previously at another hospital for a fibroid uterus. When the abdomen was opened it was decided that the patient was pregnant and did not have a fibroid. She continued to have menstrual periods postoperatively and became pregnant three months after operation. The fibroid seemed to enlarge during pregnancy but caused no particular symptoms.



Fig. 1.—Photograph of specimen showing uterus, tube, ovary, and fibromyoma. The split in the serosa is readily seen posterior to the tube and ovary.

She had a normal spontaneous delivery of a 6 pound, 9 ounce, living female infant four hours after entering the hospital. Pituitrin and Ergotrate were given after the

*Presented at a meeting of the Chicago Gynecological Society, March 18, 1955.

placenta was expressed. The uterine cavity was explored for tears and retained tissue. The large fundal fibroid was noted. It did not encroach upon the uterine cavity. Postpartum bleeding was not excessive and the patient was put to bed.

Three hours later the patient was noted having difficulty in breathing. The peripheral pulse and blood pressure were unobtainable. No gross external hemorrhage was present but a dilute intravenous Pituitrin drip was started. The patient was returned to the delivery room for re-examination while blood was obtained. The abdomen was definitely distended and soft. No fluid wave could be detected. The fibroid seemed unchanged and not tender. Vaginal and uterine examination were repeated but no rent or retained placenta was found. Bizarre medical causes of postpartum shock were discussed. A colpocentesis was decided as the simplest method to prove intraperitoneal hemorrhage and this was done with ease. Nonclotting blood was aspirated and the patient was prepared for operation.

She was operated upon after blood transfusions had brought the blood pressure up to 95/70. The abdomen contained about 2,000 c.c. of free blood. The fibroid occupied the posterior fundal area. The surface of the uterus was split as if a transverse incision had been made through the serosa and outer muscle down to an intramural fibroid. Blood was flowing from the edges of the torn serosa. A subtotal hysterectomy and right salpingo-oophorectomy were done. She was given a total of 5 pints of blood. Penicillin was given prophylactically. The postoperative course was uneventful and she went home on the sixth day. The pathologist reported that the uterus contained a fundal fibroid which measured 18.0 cm. in diameter (Fig. 1).

Comment

It is interesting to speculate why such a complication should occur. The fact that she had been operated upon one year previously sheds some light. The fibroid must have been soft, fundal, intramural, and causing no obvious distortion of the round ligaments or insertion of the tubes. The fibroid caused no complications during pregnancy. During and after delivery the uterine musculature contracted and the fibroid was squeezed out of the fundus as one would squeeze the pit out of a cherry.

The colpocentesis was of value in that the diagnosis of intraperitoneal hemorrhage was confirmed and no further delay incurred while waiting for further medical workup.

Despite one ovary and tube left in situ, the patient began complaining of hot flashes six months after operation. Her symptoms have been relieved by oral stilbestrol.

Summary

A case of a known fibroid complicating pregnancy has been presented. Delivery was uneventful but bleeding resulting from partial spontaneous enucleation occurred, necessitating operation.

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EARLY REMOVAL OF THE CORPUS LUTEUM IN A TRIPLE PREGNANCY

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THERE have been conflicting reports regarding the effect on pregnancy of early removal of the corpus luteum. One contention, largely based on the work of Fränkel,¹ holds that the corpus luteum is indispensable for the maintenance of the pregnancy through the end of the first trimester. In opposition to this view, many investigators including Glasser,² Michaels,³ and Greenhill⁴ have supported the conclusion reached by Simmonet and Robey⁵ following their review of all available literature on the subject in 1939. This view holds that removal of the corpus luteum may be performed at any time without disturbing the pregnancy.

The following report represents a rather unusual case of early removal of the corpus luteum and presents a strong argument for the latter view.

Case Report

C. P., a 27-year-old para ii, was admitted to the Centre County Hospital, April 14, 1954. Her last menstrual period had occurred Feb. 3, 1954. Approximately two weeks prior to this admission she noted the onset of a dull pain over the lower abdomen which became progressively more severe. A pelvic examination performed at this admission demonstrated a soft, discolored cervix with an enlarged uterus and a soft, symmetrical, fluctuant mass in the cul-de-sac posterior to the uterine body which produced extreme pain to bimanual palpation. The presumptive diagnosis was an ovarian cyst with possible torsion of the pedicle, and the patient was operated upon on April 16, 1954. On visualization of the pelvis, the uterus was found to be enlarged to the size of an eight weeks' pregnancy, and there was a corpus luteum cyst of the right ovary approximately 8 to 10 cm. in diameter in the cul-de-sac. There was no evidence of impaired blood supply or torsion of the pedicle, but in view of the size of the cyst and the severity of the pain it was elected to perform a right oophorectomy. The patient was placed on 200 mg. of progesterone daily but developed a sensitivity reaction to the injections and the drug was stopped on the sixth postoperative day. A fecal impaction caused the patient much distress on the fifth postoperative day and resulted in a twelve-hour period of severe crampy pains over the lower abdomen which were thought at first to be the result of uterine contractions and a threat to the pregnancy. The impaction was broken up with difficulty and the remainder of her convalescence was uneventful. The pathological report confirmed the diagnosis of a corpus luteum cyst.

Following the patient's return home from the hospital, she had an essentially normal antepartum course through Sept. 5, 1954, at which time she suddenly went into labor and three hours later delivered triplets after having received a pudendal block. The first child was delivered spontaneously and the other two were delivered by outlet forceps over a midline episiotomy. The infants ranged in weight from 3 pounds, 2 ounces, to 3 pounds, 8 ounces, and all appeared in satisfactory condition immediately following delivery. One infant suddenly developed cyanosis 24 hours after birth and died shortly thereafter. The

second child died 48 hours later, and the last child on the sixth postpartum day. The autopsy reports on all these infants demonstrated pulmonary hemorrhage of intra-alveolar type, possibly due to inhalation.

Comment

In a review of the world literature, this appears to be the first case of early removal of the corpus luteum in a triplet pregnancy. It is well known that there is a high incidence of spontaneous abortion in the uncomplicated triplet pregnancy, and yet early removal of the corpus luteum had no demonstrable detrimental effect on this pregnancy. It appears that this case presents convincing evidence that the corpus luteum is not necessary for maintenance of pregnancy in the first trimester. There also appears to be reasonable doubt concerning the necessity for supplementary progesterone therapy in these cases.

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A PRELIMINARY REPORT ON TYPHOID, TYPHUS, TETANUS, AND CHOLERA IMMUNIZATIONS DURING PREGNANCY

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THE increased fetal mortality incident to cholera, typhoid fever, or tetanus complicating pregnancy is well known; however, little has been published on the incidence of complications of pregnancy following immunizations against these diseases. Eastman¹ states that Sauramo has found abortions frequently follow typhoid injections during the first half of pregnancy. Eastman himself reports 2 cases in which abortion promptly followed either the first or second typhoid injection. The published reports on vaccination during pregnancy are more than adequate. Lieberman² vaccinated 351 pregnant women without ill effects and Urner³ vaccinated 129 pregnant women without noting a single instance of threatened abortion, miscarriage, or premature labor.

A review of 107 patients who received immunization injections during pregnancy was made at the 6110th USAF Hospital during the twelve-month period, January, 1954, through January, 1955. The initial immunizations administered were cholera, typhoid, typhus, and tetanus. The booster injections were typhoid, typhus, and tetanus. Of the total 107 cases, 45 were initial immunizations and 62 were booster injections. Vaccinations have been omitted in this report.

The initial immunizations were administered to pregnant Japanese women married to United States servicemen. The booster injections were administered primarily to military dependents who had received their initial injections prior to overseas travel and prior to pregnancy. For the purposes of this paper the immunized group will include those receiving the booster injections as well as those receiving the initial injections.

Thirty-seven of the 45 women who received initial immunizations have gone to term without complications except for pre-eclampsia in 2 cases and threatened abortion in one. The threatened abortion occurred 3 weeks after the immunizing injections were completed. Five women are presently in the last trimester and without complication thus far. One patient required a right salpingectomy for an ectopic pregnancy. Another developed severe pre-eclampsia in the last trimester and was delivered of a premature infant that did not survive. The pre-eclampsia developed 6 months after the initial injections were completed.

Sixty-two pregnant women received booster injections and, of these, 48 have reached term without complications other than mild pre-eclampsia in 4 cases. One woman had spontaneous rupture of the membranes at 36 weeks and was delivered of a viable premature infant. Nine are in the last trimester

without complications thus far and 4 have had spontaneous abortions. The abortions occurred at 5, 8, and 13 weeks after the booster injections were administered.

Localized swelling and tenderness at the site of injection and mild generalized malaise were most commonly encountered following the typhoid and cholera injections. The incidence of these signs and symptoms was not recorded. In only 2 instances were the symptoms severe enough for the patient to present herself at the hospital clinic. Both went on to term without further complications.

As shown in Table I, the initial injections and booster injections were administered for the most part in the first and second trimesters. In parentheses are the numbers of abortions that occurred during the respective trimester.

TABLE I. SUMMARY OF TIME OF ADMINISTRATION OF INJECTIONS

| | TRIMESTER | | |
|--------------------|-----------|--------|-------|
| | FIRST | SECOND | THIRD |
| Initial injections | 26 (0) | 17 (0) | 2 |
| Booster injections | 26 (2) | 27 (1) | 9 |

During the same reporting period there were 129 pregnant women seen in this clinic who did not receive immunization injections. Eighty-eight have come to term and been delivered, 31 are presently in either the second or third trimester, and 9 underwent spontaneous abortions. One woman was delivered of twins at 38 weeks by cesarean section (1 living, 1 stillborn). Of the 88 term pregnancies there were 6 complicated by pre-eclampsia. The twin pregnancy was also complicated by pre-eclampsia. Of the 31 patients not yet delivered, there are 3 who have pre-eclampsia, one of whom also has diabetes. One patient with a term pregnancy had cesarean section for a transverse lie and another suffered hemorrhage in the third stage from a partially separated placenta. The incidence of abortion in the control group is approximately 7 per cent in the group that received the immunization injections it is approximately 5 per cent. The incidence of toxemia in the two groups, considering only those women who have been delivered is approximately 8 and 7 per cent, respectively.

A pregnancy was considered uncomplicated if the woman was delivered of a living infant at term without suffering threatened abortion, toxemia, hemorrhage, or infection during pregnancy, labor, or the puerperium. Since the two groups are similar in most respects, the incidence of total complications applies to all the cases reported, both delivered and undelivered. The approximate incidence of complications in each group thus far is shown in Table II.

TABLE II. INCIDENCE OF COMPLICATIONS IN IMMUNIZED AND CONTROL GROUPS

| | SPONTANEOUS ABORTION | TOXEMIAS | TOTAL COMPLICATIONS |
|-----------|-------------------------|----------|------------------------|
| Immunized | 5% | 7% | 13% |
| Control | 7% | 8% | 16% |

The incidence of abortion and other complications is presented for the sole purpose of comparing two similar groups of patients managed in the same hospital and differing primarily in that one group received immunization injections and the other did not. In the total 107 cases in which injections were given,

there were no abortions immediately following and, other than the symptoms previously mentioned, there were no complications of pregnancy which could be directly attributed to the injections. Thus far the incidence of abortion, toxemia, and other complications of pregnancy has been no higher in this group than in the group of pregnant women who did not receive immunization injections.

Summary

1. A preliminary report of 107 cases in which immunization injections were given during pregnancy has been presented. Initial immunizations against cholera, typhoid, typhus, and tetanus were given in 45 cases and booster injections for typhoid, typhus, and tetanus in 62 cases.

2. There were no instances of abortion immediately following any of the injections. The incidence of complications of pregnancy in this group has been no higher than in the group of pregnant women who did not receive immunization injections.

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MELANOMA OF THE VAGINA AND CERVIX TREATED BY RADICAL SURGERY

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MELANOMA of the vagina and cervix is always secondary, usually to melanoma of the vulva. The latter may be cured by excision before metastasis has occurred. No successfully treated case of vaginal or cervical melanoma can be found in the literature, however. The following is a case of extensive metastatic melanoma of the vagina and cervix treated by radical surgery four years ago, with successful outcome to date.

Case History

G. T. (Case No. 335046, Strong Memorial Hospital) was a 29-year-old white married housewife, para iii, gravida iii, first seen in another city on Oct. 3, 1949, with a pigmented nevus of the left labium majus. This was excised on Nov. 15, 1949; microscopic sections disclosed a melanoma. Two years later, the patient was seen with an attack of acute cholecystitis, and on Sept. 21, 1951, a cholecystectomy was done. At the time of this operation, pelvic examination showed black spots on the vagina and cervix. Multiple biopsies of these areas revealed metastatic melanoma in all sections, and the patient was referred here for treatment.

A survey for metastases showed no evidence of tumor in the lungs or osseous system. Cystoscopic and sigmoidoscopic examinations revealed no metastases in the bladder or lower bowel. During the period of diagnostic work-up in the hospital, actual downward extension of the melanoma in the vaginal wall was noted, the latter becoming almost entirely coal-black in appearance, with scattered patches of normal-colored vagina. The vulval area where the primary melanoma had been excised showed only a small, puckered scar, with no pigmentation or induration.

On Oct. 15, 1951, an abdominoperineal resection of the entire genital tract was carried out. This consisted of en bloc radical hysterectomy, gland dissection, vaginectomy and radical vulvectomy, done in continuity. The abdominal phase consisted of the same dissection as done in the operation for cancer of the cervix, except that the vagina was not transected. The abdominal incision was then closed and the patient was placed in exaggerated lithotomy position. A radical vulvectomy was then begun, this dissection being carried up to meet that from above. The entire specimen was removed from below. The urethral wall was immediately adjacent to extensive melanoma on the anterior vaginal wall and was removed with the vagina. Pathologic sections showed melanoma throughout the vaginal wall and cervix, but none in the primary vulval site. The pelvic lymph nodes showed no metastases. The patient did well postoperatively. A permanent suprapubic cystostomy was subsequently established, since reconstruction of the urethra was not feasible.

When last seen, over three years since operation, the patient presented an appearance of excellent general health, with no evidence of recurrence or metastases. Construction of an artificial vagina for coital function is planned for the near future.

Summary

A case of metastatic melanoma of the vagina and cervix is presented, with four-year survival to date, treated by an abdominoperineal resection. This combined approach allowed a radical hysterectomy, vaginectomy, and vulvectomy to be done in continuity.

A VERY EARLY CASE OF CARCINOMA OF BARTHOLIN'S GLAND

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PRIMARY malignancies of Bartholin's gland are relatively rare, and one usually has a false impression of benignity when a firm or cystic mass is felt in this location. Patients rarely exhibit concern unless severe pruritus, swelling, pain, or discharge calls attention to a lesion in the area where Bartholin's gland is located. These symptoms and signs are actually *late* signs of carcinoma of Bartholin's gland. Even though relatively rare, these malignant neoplasms have an amazingly high mortality rate. Bowing, Fricke, and Kennedy³ report that, in a 37 year period (1910-1947) at the Mayo Clinic, there were 700 benign lesions of Bartholin's gland treated surgically, and only 7 primary malignancies of the gland found, thus showing the incidence of malignancy to be 1 per cent. Wharton and Everett's¹⁶ excellent paper in 1951 is the latest compilation of cases from the literature and presents 109 cases. Illustrative of the serious character of the lesion is the fact that of the 109 cases presented with their varied treatments, only 9 had five years or more of survival, in spite of the added fact that the average age incidence is reported as 49.6 years. Rabson and Meeker¹² reported an average "patient lag" of 15 months before reporting to the physician for treatment. Undoubtedly, more time is lost by "physician lag" due to lack of realization that such lesions must be investigated immediately to give the patient any chance at all. Only 9 of the 109 cases reported by Wharton and Everett had histories of bartholinitis in the past, which indicates that inflammation is, at the most, only a minor etiological factor. This, coupled with the fact that the symptoms of tenderness, mass, pruritus, and discharge are the usual ones seen in bartholinitis as well as in malignancy of the gland, makes the situation very dangerous for the patient, as local therapy and reassurance as to benignity will likely come before investigation. Microscopically, 46.8 per cent of the carcinomas of Bartholin's gland are adenocarcinomas, and 35.8 per cent are squamous-cell carcinomas. The remaining 17.4 per cent are mixed, with 7.3 per cent being variable forms of carcinoma, 3.7 per cent being sarcoma, and 6.4 per cent being undifferentiated or unknown.

As is true of most vulvar malignancies, these lesions apparently metastasize early, both by direct extension and to the inguinal and femoral glands bilaterally. The majority opinion is that radical vulvectomy, followed by extraperitoneal Bassett gland dissection, gives the best results. Opinion is divided as to whether unilateral or bilateral vulvectomy is the procedure of choice. Surgical therapy should be followed by deep x-ray therapy if the

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lesion seems to be extensive. Taussig¹⁵ felt that the gland dissection should precede the vulvectomy, and this thought is shared by others. The rarity of the lesion and the inability to concentrate statistics have prohibited a really definite plan of therapy. Bowing, Fricke, and Kennedy³ report the use of radium in these lesions, both as palliative therapy for advanced lesions and adjunctive therapy, along with surgery, for less advanced lesions. Rabson and Meeker¹² enhanced the position of radiotherapy in the treatment of this disease by noting the fact that in their series no patients had survived longer than three and one-half years without supplemental radiotherapy.

Even though advanced, the local lesions may appear deceptively benign. Pund and Coles¹¹ in presenting a case seen at autopsy pointed out that it had been diagnosed as lymphogranuloma venereum because of the striking resemblance to it, in spite of repeatedly negative Frei tests.

Case Report

Patient No. 504-1954, gravida viii, para vi, aged 55 years, was first seen in the medical outpatient clinic at St. Joseph's Infirmary on Dec. 21, 1953. Her chief complaints were epigastric distress, occasional episodes of nausea and vomiting, and intolerance to fats. During the physical examination, a rather firm, nontender mass 3 cm. in diameter was found in the left labium majus. This mass had been present for approximately six months without producing any distress. The mass was deep in the tissue, was located in the area where Bartholin's gland is usually found, and seemed to be connected to the duct of Bartholin's gland; thus, three of the four criteria presented by Honan in 1897 for the diagnosis of tumors of Bartholin's gland were satisfied. It was semicystic.

On Feb. 10, 1954, a cholecystectomy and left bartholinectomy were done. Report of the microscopic examination of the excised mass was as follows: "The sections of this Bartholin cyst show the wall to contain typical fibrous tissue. Part of the Bartholin cyst lining is made up of stratified squamous epithelium. This layer is thin but does not invade. It consists of young, rather poorly differentiated epithelial cells. These do not mature in a normal fashion. In one end of the cyst, they are in a thicker layer than elsewhere. They contain dark, deeply stained nuclei, with a number of mitoses in each field. This is an early low-grade malignancy. In other places, the lining is replaced by granulation tissue." Her course following this operation was uneventful and she was discharged from the hospital on Feb. 18, 1954.

Discussion of her case in the tumor clinic resulted in a majority opinion in favor of treating the malignancy by radical vulvectomy, followed by Bassett type inguinal and femoral lymph node dissection. The decision was based on the high degree of malignancy of these cancers. It was made in spite of the fact that this seemed to be a limited type of lesion. On March 8, 1954, the patient was admitted to the hospital. On March 9, 1954, a radical vulvectomy was done on the left, removing the lower half of the vagina and carrying the deep dissection into the ischiorectal space, and excising the lateral third of the anal sphincter. A simple vulvectomy was performed on the right. She was discharged on March 28, 1954, the twentieth postoperative day. On April 10, 1954, the patient was readmitted for the Bassett procedure. This was done on April 12, 1954, and she tolerated the operative procedure well. Postoperatively, there was an episode of thrombophlebitis which was controlled by the use of anticoagulants, bed rest, and elevation of the extremities. Postoperative sequelae were moderate edema of the feet and cramping of the legs when erect for extended periods. Her inguinal wounds healed by secondary intention; the use of local enzyme therapy enhanced the final healing of these wounds.

The tissue from both the vulvectomy and the radical inguinal and femoral node dissection was negative for tumor tissue and the glands were reported as showing chronic

lymphadenitis. Early ambulation was used in all postoperative periods. The patient was discharged from the hospital on May 28, 1954, the forty-sixth postoperative day.

Summary

A brief review of the literature concerning malignancy of Bartholin's gland is discussed. A case of epidermoid carcinoma of Bartholin's gland, which was discovered unusually early, is added to the literature.

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DESCRIPTION OF A THECA-CELL TUMOR IN 1926

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A REVIEW of the cases of theca-cell tumors in our files reveals a tumor diagnosed pathologically as "benign solid ovarian tumor of theca lutein origin" by Drs. D. Anthony D'Esopo and William Johnson. This case was presented before the New York Pathological Society on Oct. 14, 1926. In the discussion following the presentation of the paper, the members present characterized the tumor incorrectly as an ovarian sarcoma. It was never published, although it appears on the program and in the minutes of the New York Pathological Society.¹

The first published description of a thecoma appeared in 1932 by Loeffler and Priesel,² who individualized the tumor with the descriptive name of "Fibroma Theca Cellulari Xanthomatodes." Due to the similarity of thecomas to ovarian fibromas these tumors were previously classified under the headings of "fibroma of the ovary," "fibroadenoma of the ovary," or "fibrosarcoma of the ovary."

Case Report

Case No. 9440 and Pathology No. 1905 (Sloane Hospital for Women). Mrs. H. R. was admitted to the hospital Sept. 8, 1926. She was a 58-year-old white married para i, gravida iii. The chief complaint was postmenopausal bleeding for one year. Examination revealed a fibroid uterus. The operation on Sept. 9, 1926, consisted of a dilatation and curettage, a supravaginal hysterectomy, and bilateral salpingo-oophorectomy. The pathological report was: uterus, cystic glandular hyperplasia of the endometrium and intramural fibromyomas; right ovary, a solid benign tumor of theca lutein cell origin. The left ovary was atrophied and the Fallopian tubes were fibrosed. The following is a description of the right ovary:

"Grossly the right ovary is globular and has a firmer consistency than usual. It measures 4 by 3.5 by 2.5 cm. Its upper pole shows many firm warty masses which protrude over the general surface of the ovary. They appear yellowish in color. The ovary in section is firmer than usual. On section it is found that the yellow nodules noted externally protrude into the cortex. There are also several firm yellow nodules in the substance of the ovary which do not come to the outside.

"Microscopically the firm yellow masses noted grossly show varied types of cells arranged in circular masses surrounded by ovarian stroma. The tumor is cellular and stains deeply. Majority of the cells are spindle shaped. Others are irregularly rounded and in a few places are found larger polyhedral cells. Sudan stain for fat showed presence of globules in many of the cells, but more pronounced in the larger polygonal cells. The fat is double refracting when observed under the polarizing microscope. Stain for iron shows no pigment. Van Gieson stain shows large amount of connective tissue in capsule but only a few fine strands in the tumor itself. Large amount of reticulum is found between the individual cells. No mitotic figures are found."

The photographs in Figs. 1-4 have been made from the original negatives of the endometrium, and the right ovary. The negatives are from the pathological files and were presented as lantern slides before the New York Pathological Society in 1926.

The clinical history, the operative and pathological findings leave no doubt that this was a case of a theca-cell tumor.

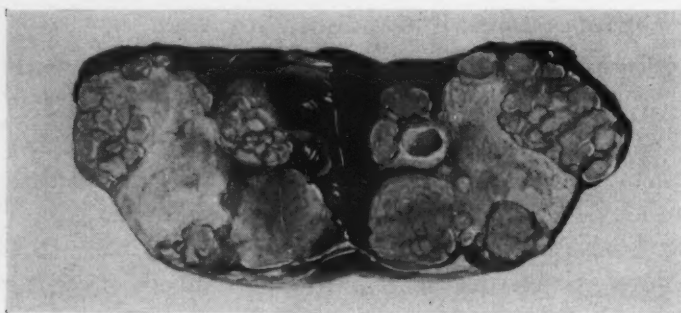


Fig. 1.—Gross appearance of the right ovary on sagittal section. Note the circumscribed nodules of tumor tissue.

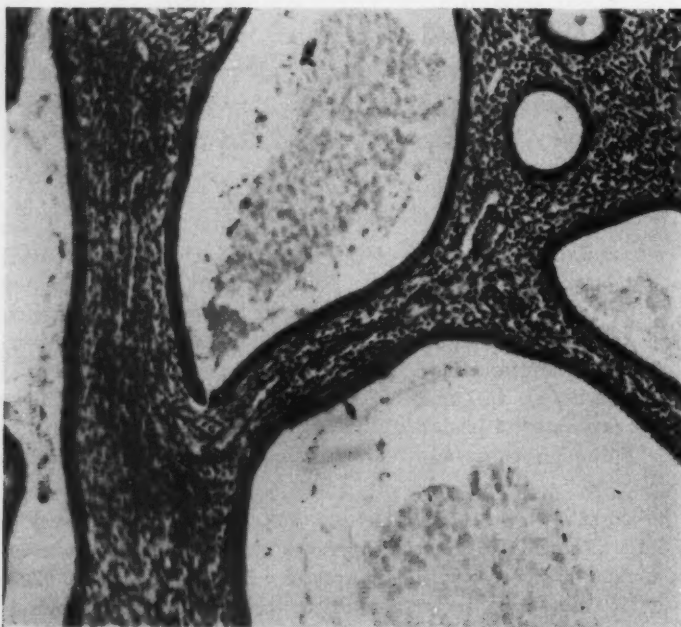


Fig. 2.—Cystic glandular hyperplasia of the endometrium associated with the thecoma.

Summary

1. An acknowledgment is made of a hitherto unpublished description of an ovarian tumor of theca-cell type by Drs. D. A. D'Esopo and W. Johnson in 1926.
2. The case upon which the description of D'Esopo and Johnson is based is presented together with a photograph and photomicrographs.

Fig. 3.

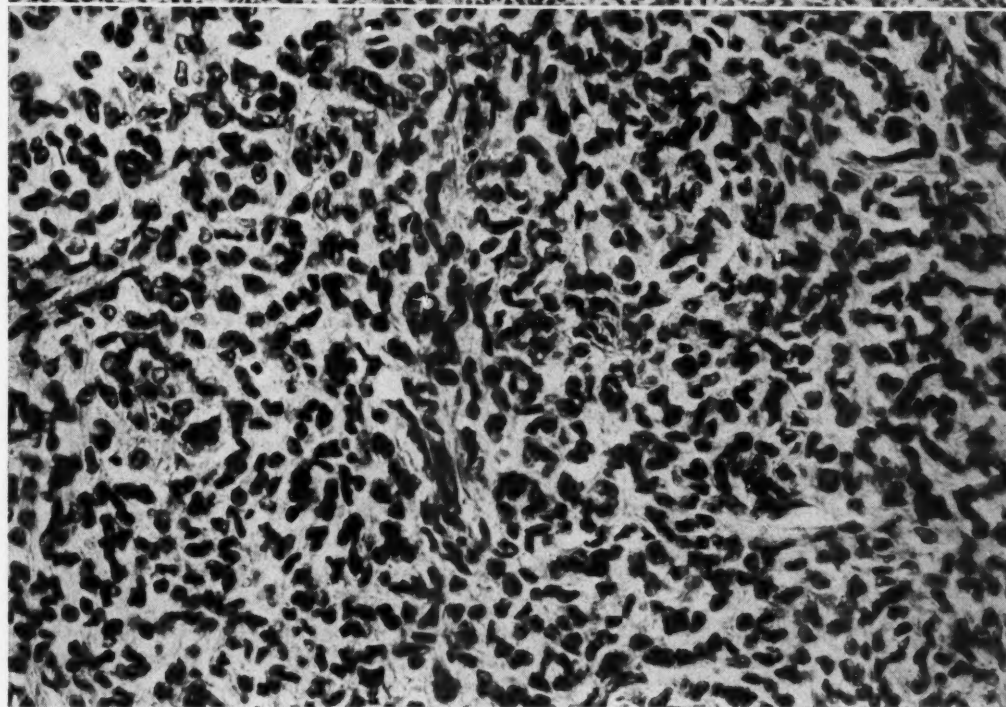
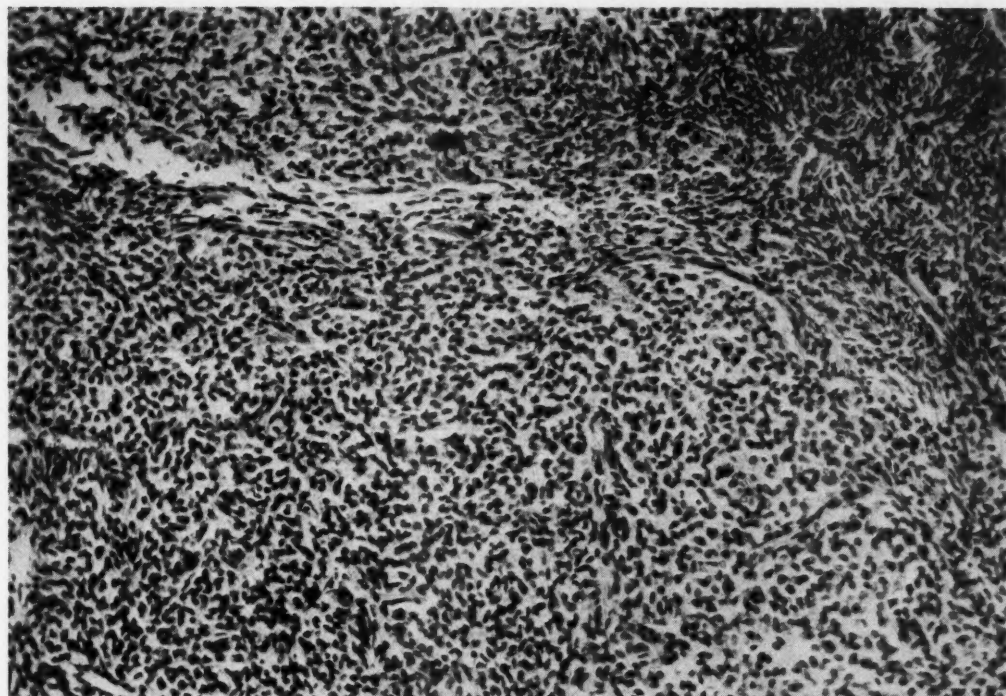


Fig. 4.

Fig. 3.—Thecoma of the right ovary. ($\times 200$.)

Fig. 4.—Thecoma of the right ovary. ($\times 450$.)

The assistance of Miss Gladys Warburton, the recording secretary of the New York Pathological Society, and Dr. Virginia Franz, of the College of Physicians and Surgeons, Columbia University, also past president of the New York Pathological Society, is acknowledged in locating and searching the records of the Society. The assistance of Dr. Earl T. Engle, of the College of Physicians and Surgeons, Columbia University, in reviewing the microscopic sections of this case is acknowledged.

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RUPTURED SUPPURATING MYOMA

A Surgical Emergency

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AN UNUSUAL abdominal emergency was seen recently on the Gynecological Service of Albany Hospital. Exploratory laparotomy disclosed the cause to be the spontaneous intra-abdominal rupture of a suppurating uterine myoma.

Case Report

The patient, a 50-year-old white single secretary, was admitted to the emergency suite complaining of severe, sharp low abdominal pain which had had a sudden onset 4 hours prior to admission, with associated nausea and vomiting. On examination there were marked spasm, tenderness, and rigidity of the entire lower abdomen. Pelvic and rectal examination showed some induration posterior to the uterus, but no definite mass could be palpated because of the exquisite tenderness. The temperature was 99.6° F., the pulse 120, respirations 34, and the blood pressure 100/65.

Past history disclosed that a nephrolithotomy had been performed in 1947 for a stag-horn calculus of the right kidney. Three months previous to the present admission, a ureteral calculus had been removed by cystoscopy, at which time the pelvic examination was described as negative. In the interim, the patient had noted amenorrhea and persistent mild abdominal pains until the onset of the present illness.

The usual laboratory examinations were obtained. Urinalysis was negative. The blood count showed 11 Gm. of hemoglobin, a hematocrit of 38, a white count of 12,800 with 20 band cells and 73 segmented cells. The blood nonprotein nitrogen was 44; a guaiac test on the stomach contents was 4 plus.*

Shortly after admission an exploratory laparotomy was performed. The peritoneal cavity contained a large amount of purulent exudate arising from a 3 cm. perforation of what was at first sight believed to be an infected ovarian cyst or tuboovarian abscess. Further inspection showed that the adnexa were normal, and that the uterus itself was the site of rupture. The impression then was that the origin was a pyometra. Panhysterec-tomy and bilateral salpingo-oophorectomy were performed, and the peritoneal cavity drained through the vagina.

Gross examination of the specimen showed an unsuspected intramural suppurating myoma 7 cm. in diameter, occupying the posterior surface of the fundus, and completely separate from the uterine cavity. The thinned wall of the abscess cavity was the site of the serosal laceration. Histologic examination confirmed the gross diagnosis. Bacteriologic culture disclosed that a member of the coliform group was the offending organism. Except for transient jaundice resulting from blood transfusions, the recovery was straightforward. Tetracycline was administered for one week, and the patient was discharged in good condition on the twelfth postoperative day.

*The positive guaiac test was believed to be the result of forced vomiting.

Comment

Suppuration in a myoma is an infrequent occurrence.¹⁻¹⁰ Guéry⁵ in 1901 collected 47 cases of genuine suppuration. Miller,⁸ in 1945, was able to find only 75 such cases reported since 1871. In differentiating suppuration from degenerative liquefaction, various authors^{5, 7} have stressed the importance of bacteriologic and histologic confirmation.

Occasionally a "pyomyoma" may rupture into the bowel, bladder, uterine or peritoneal cavities.^{4, 5, 7, 8} Ricci¹¹ listed only 13 such case reports as ours from 1800 to 1900. From then until the present time, we were able to find but 3 additional reports of similar cases in English language journals,^{12, 13, 14} although Miller⁸ mentioned Buman's case from Switzerland in his report in 1945.

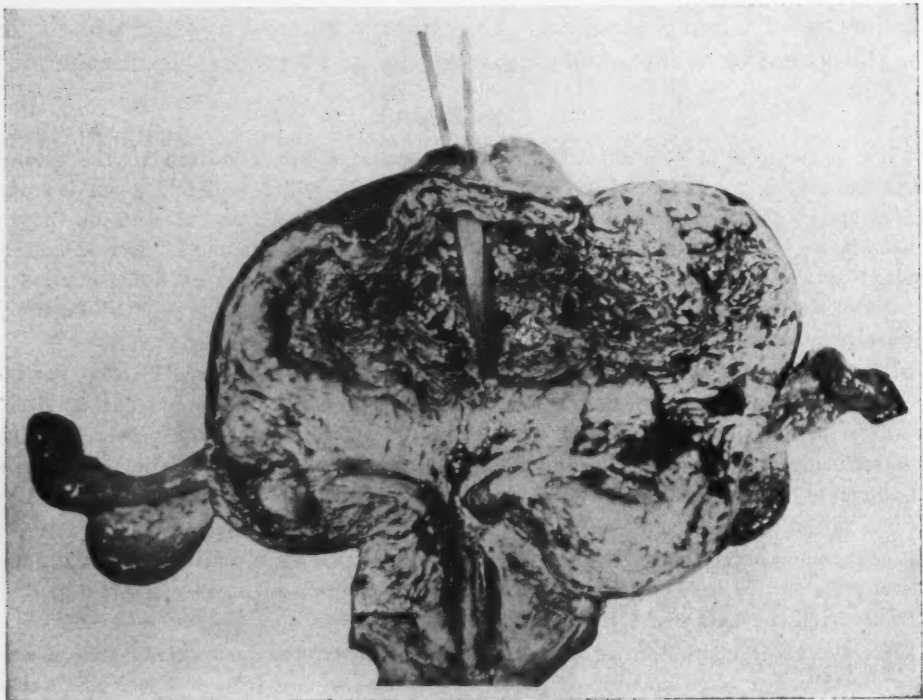


Fig. 1.—Opened uterus, showing site of rupture.

Summary

We have presented an extremely unusual cause for an acute abdominal emergency, namely, a rupture of an abscess developing in a myoma. We were able to find only 17 similar cases reported in the literature since 1800.

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TRICHOMONAS VAGINALIS VAGINITIS

A Clinical Study of 100 Cases

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ONE hundred cases of *Trichomonas vaginalis* vaginitis from private practice, and from the charity obstetrical and gynecological clinics comprise this study. All of these patients showed positive active *Trichomonas*. There was a 100 per cent follow-up. Diagnosis in each case was made by saturating a small cotton swab in the vaginal discharge and immersing the swab in 2 c.c. of normal saline. In an effort to estimate the severity of the infection, the following system was used to estimate the number of protozoa present.

A standard medicine dropper is filled with the suspension and a single drop is gently spread on a clean glass slide. A diagnosis can be made under low magnification. If trichomonads are present, a rough quantitative estimate of the severity of infection, correlated with the known clinical appearance of the vaginal tract, can also be obtained. In 1 plus grading there are one to twenty active organisms per low-power field; 2 plus, from twenty-one to forty; 3 plus, forty-one to sixty; and a 4 plus field shows sixty-one to innumerable.

A "cure" of *Trichomonas vaginalis* vaginitis is defined as two or more negative suspensions obtained at three-week intervals for at least six weeks from the last day of treatment. A failure is defined as the inability to eradicate the disease after at least twelve consecutive weeks of therapy.

Treatment

Treatment is simple and inexpensive. One hundred cases of proved *Trichomonas vaginalis* vaginitis were treated with Lautric,* a preparation containing sodium alkyl sulfate. Each bottle contains 60 c.c. of the syrupy medication. The following written instructions are given to each infected patient.

Treatment Instructions.—

1. Mix 1 teaspoonful of the medication with 1 quart of warm water in a pan. Stir until the solution is foamy. Pour into a douche bag.
2. Lie on your back in the bathtub or over a bedpan. Insert the douche nozzle deep into the vagina.
3. *Important:* Hold the douche bag by the ring on top so that the bottom of the bag will be about twelve inches above the abdomen. Open the clamp and allow the solution to run slowly into the vagina.

*Lautric was supplied by Mr. T. D. Williams, President, Gynecological Specialties, Inc., East Alton, Ill.

Lautric paste contains a highly purified sodium alkyl sulfate (where the alkyl group has an average chain of 12), with an ammonium salt added to regulate the pH as near as possible to 7.

The complete chemical formula is

$\text{CH}_3 (\text{CH}_2)_{10} \text{CH}_2 \text{O SO}_3 \text{Na}$ plus 1% sodium propionate.

4. The bottle contains sufficient medication to prepare about twelve douches. Douche morning and night for about six days.

5. *Very important:* Four days after finishing the treatment return for re-examination. In order to be sure you are improving, two more examinations are indicated after finishing the medication. Report any discharge, itching, or irritation at each examination.

Results

There were 68 gynecological patients and 32 pregnant patients in this series. Treatment was instituted during pregnancy when the diagnosis was made up to the thirty-seventh week. Nine pregnant patients had persistent infection at the end of the thirty-sixth week of gestation when treatment was suspended. Six weeks post partum the same treatment was resumed in this group, but 3 cases failed to respond and are listed as *failures*. A cure rate of 72 per cent was obtained in the pregnant group before the thirty-sixth week. Contrary to general opinion every positive case during pregnancy to the thirty-seventh week of gestation should be treated.

There were 13 postmenopausal patients, all cured. Six were also treated with vaginal estrogenic cream because of the marked symptomatic vaginitis. This should not constitute a regular adjunct to the primary treatment, because 87 per cent of all the patients had a normal supply of natural estrogens.

All but 16 of the patients had had from one to eleven pregnancies, or were pregnant at the time treatment begun. The total over-all cure rate was 92 per cent. Three of the 8 failures were in postpartum patients as noted above. Seven per cent of the cured patients had a single recurrence, but were adequately re-treated, and again cured. These are considered in the average grouping later.

Two patients had a mixed *Trichomonas* and *Monilia albicans* infection. They were treated primarily for the protozoan infection and cured, but yeast persisted and with therapy for the latter infection both patients were cured.

One of our patients had a *Trichomonas* cystitis. In 8 patients the organism was obtained from the endocervical canal by aspiration into a sterile glass pipette through the previous cleaned external os. Electrocoagulation of the cervix was done with recurrence or persistence of the organism post-operatively in 2 cases. These 2 cases are classified in our *failure* group. Skenitis or Bartholinitis due to *Trichomonas* was not observed in this study.

In all persistent cases, the male partner should be examined by the urologist. Seven uncircumcised husbands were examined by a urologist, and active trichomonads were found in the prostatic secretion in one; in smegma beneath the prepuce in another.

Lautrie used in this study produced no allergic manifestations. The only side reactions noted consisted of a burning sensation at the introitus as the douche solution escaped the vagina. This was expected in many cases due to the severity of the irritation of the vulva. No patient failed to finish the prescribed therapy because of this complaint.

It is interesting to note that 54 per cent of the patients had used other medications for the vaginitis, consisting of powder insufflation, vaginal wafers, jellies, etc. The remaining patients had used no specific medication, or simply douches for symptomatic relief.

The distribution of the classical triad of symptoms—leukorrhea, pruritus, and irritation of the vulva—was as follows:

Leukorrhea and pruritus, 17 per cent.

Leukorrhea, pruritus, and irritation of the vulva, 64 per cent.

Leukorrhea only, 10 per cent.

Pruritus only, 2 per cent.
Asymptomatic, 7 per cent.

The duration of one or more symptoms of the triad prior to treatment with Lautric was from two days to eleven years; 2 patients gave a history of having had *Trichomonas vaginalis* vaginitis for eight years.

The average amount of medication required to obtain a cure and the average duration of treatment to obtain a cure are shown in relation to the grading of the infection in Table I.

TABLE I

| GROUP GRADING | NO. PATIENTS | AVERAGE AMOUNT OF LAUTRIC (NO. OF 2 OUNCE BOTTLES) | AVERAGE NO. OF DAYS FROM LAST TREATMENT TO DAY OF SECOND NEGATIVE SUSPENSION |
|------------------------|--------------|--|--|
| 1 plus | 8 | 3.01 | 47.0* |
| 2 plus | 30 | 2.70 | 36.3* |
| 3 plus | 26 | 3.63 | 40.4 |
| 4 plus | 28 | 5.00 | 50.3 |
| Failures, 3 and 4 plus | 8 | 11.30 | 84 and more |

The patient returns for re-examination four days after completing the treatment for the first check. If this is negative for Trichomonads, no further therapy is rendered. She returns approximately three weeks later for a second examination. If this is also negative the least total number of days from the last treatment to the second suspension is twenty-five days. A third and final negative suspension constitutes our criterion for cure.

Many of our patients in each group were free of the parasite on the first, second, and third examinations after using only a single 2 ounce bottle of the medication. Seven patients had a single recurrence; in 6 pregnant patients treatment was temporarily discontinued due to the nearness of term, but they were cured post partum.*

Summary

One hundred proved cases of *Trichomonas vaginalis* vaginitis with 100 per cent follow-up examination were treated with Lautric. Thirty-two patients were pregnant and were treated up to the thirty-sixth week of gestation.

It appears from this study that the higher the grading, the longer the time required for a cure; therefore, the greater the quantity of medication required.

One patient was discovered to have carcinoma of the cervix at the six weeks post partum checkup. She was cured of *Trichomonas* vaginitis before delivery.

One pregnant patient aborted at fourteen weeks. Treatment with Lautric was not felt to have been contributory, because a postabortal cure was obtained. This patient was carefully studied for evidence of toxic or allergic reactions to Lautric, but none were found.

Three of our failures still harbor trichomonads after two years in spite of all carefully considered foci of infection.

*These 13 patients were in Group 1 plus and Group 2 plus, accounting for irregularity in these averages.

Conclusions

1. Lautric, when used properly as a douche, appears to have cured 92 per cent of the patients in this series.
2. There were 8 per cent total failures.
3. Seventy-two per cent of the 32 pregnant patients were cured.
4. Over 50 per cent of our cured patients had been treated with various medications previous to treatment with Lautric.
5. No toxic or allergic manifestations were encountered in this series.
6. A method of estimation of the severity of the infection is correlated with the average amount of medication, and the duration of time required for a cure.

1509 FOURTH AVENUE

BARTHOLINITIS SIMULATED BY ANAL INFECTION*

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THE purpose of this brief presentation is to invite the attention of the profession to an entity which, although proctologic, presents the appearance of bartholinitis and may be misleading to the gynecologist. It is noteworthy that no previous description is to be found in the medical literature from the year 1879.

Anorectal suppurations usually arise in the crypts of Morgagni. These are small pouches at the dentate line, or mucocutaneous junction, whose mouths look upward, and they are therefore accessible to receive and retain infectious inocula. Appended to the depths of these pockets are vestigial ducts which lead, in turn, to anal glands. Both of these are true preformed structures; the glands are analogous to the preen glands of lower mammals, secreting a substance whose odor is sexually stimulating. The glands lie, in part, within the anal sphincter, and some penetrate the muscle to be situated in the ischioanal fat. Thus, an infection originating in a crypt of Morgagni is located in the associated duct. The duct, once inflamed, is occluded proximally by the resultant edema, and the pus, denied escape by way of the crypt, extends distally to involve the gland. When the latter suffers pressure, atrophy, and necrosis, the infection has been conveyed to the ischioanal fossa, or the plane of the superficial layer of the superficial fascia, immediately subjacent to the skin. Since the skin of the buttock is quite resistant, the infection may extend in the loose areolar tissue in several directions, one of which is to the scrotum or labia majora. Scrotal involvements in the male are not uncommon. Labial presentation of such suppurations is the subject of this discussion. Two illustrative cases observed and treated simultaneously by one of us (B. L.) follow.

CASE 1.—Miss B. U., aged 20 years, was first seen with a weeping sinus in the lower angle of a scar over the left Bartholin gland. The history dated back three months when an abscess of the left Bartholin gland was drained by incision. Her hymen was intact.

The sinus and gland were excised and primary healing was uneventful. Three months later, however, the original sinus recurred. In addition, a secondary sinus tract opened between the perineum and the original sinus. Both sinuses were traced by probing through a common passage into the anal canal. A diagnosis of anolabial fistula was made. Following fistulectomy, recovery was uneventful (Fig. 1).

CASE 2.—Mrs. F. C., aged 37 years, was admitted to the hospital with a diagnosis of a left ovarian cyst. At operation an endometrial cyst was found. Operative procedures consisted of a left salpingo-oophorectomy and appendectomy.

*Presented at a meeting of the Obstetrical Society of Philadelphia, March 3, 1955.

The patient gave a significant history of having had an anal fistulectomy five years previous to the present illness.

On the sixth postoperative day she complained of rectal pain and simultaneously developed a low-grade fever. Rectal examination at this time was nonrevealing. Pain and fever continued for three days when a left Bartholin abscess was first noted. This was incised, drained, and probed, with the following note made at this time: "The pus pocket was probed with a hemostat which led into the rectal canal as noted by digital rectal examination." The wound healed within two weeks, but a sinus opening at its lower angle persisted. Cure was subsequently obtained by fistulectomy.



Fig. 1.—Grooved director is shown in original sinus at lower pole of scar of incision; probe is in the secondary perineal sinus.

Comment

Diagnosis of these lesions requires the consideration of the possibility of anal origin. A history of precedent proctologic signs or symptoms is significant. Since the sensory innervation of the vulvar, perineal, and perianal areas is a common one, all deriving from the second, third, and fourth sacral nerves, via the pudendal nerves, there is poor localization and often bizarre pain reference, so that the patient's history as to the site of onset may be misleading.

On examination, the induration which involves the labium can easily be felt to cross the perineum to the buttock. Digital examination of the anus should elicit increased sphincter tonus, and reveal prominent papillae, a finding which is indicative of inflammation of the contiguous anal crypts. The

orifices of the crypts may be felt to be puckered and retracted as an evidence of repeated or long-standing infection. Pus may appear externally as the finger is withdrawn.

Speculum (anoscopy) examination of the anus should disclose the hypertrophied papillae and inflamed crypts. A probe with its tip bent to a right angle may be used delicately to find the guilty crypt; a flow of pus, of course, ends the search.

If the lesion cannot thus be decompressed, the problem as to the site of incision arises. With the index finger in the anus, the thumb will elect the point closest to that orifice, yet beyond the sphincter thickness, which will allow adequate drainage. Incision at such a point will give a short fistula, and the consequent fistulectomy or fistulotomy will be conservative and readily accomplished. Incision at a point remote from the crypt of origin needlessly complicates the subsequent definitive treatment, requiring a mutilating dissection and a much more difficult convalescence.

Should the labium be incised, an indication that the infection is of anal origin is the malodorous *Escherichia coli* pus, definitely of fecal character. If the abscess is explored by probing, the instrument will find its way to the ischioanal or even the perianal space. A final indication is the failure of the point of incision to heal, with persistent drainage from what will ultimately be recognized to be the external sinus of a fistula in ano. The continued suppuration, of course, derives from the obstinate infection in the anal crypt and its appendages, and requires fistulectomy for its interruption.

Incising the labium does no harm other than to complicate severely the removal of the tract. The plane of extension of the process in the superficial fatty fascia is external to and exempts the perineal musculature; the ultimate cosmetic derangements are of little concern.

Department of Reviews and Abstracts

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Selected Abstracts*

The Lancet

Vol. 1, January 15, 1955.

Ross, J. Cosbie, Gow, J. G., and St. Hill, C. A.: The Treatment of Genito-urinary Tuberculosis, p. 116.

Tuthill, J. F.: Impotence, p. 124.

Abbas, T. M.: Torsion of a Fallopian Tube, p. 128.

Vol. 1, January 22, 1955.

*Harris, T. A. B.: A Barbiturate Antagonist, p. 181.

Harris: Barbiturate Antagonist, p. 181.

B,B-methyl-ethyl glutarimide (designated NP 13) was discovered by Shaw, Simon, Cass, Shulman, Anster, and Nelson (Nature, London 173: 402, 1954) to be a barbiturate antagonist. The present report deals with the use of this compound in three groups of patients: (1) Fifty-seven psychiatric patients who were prepared for shock therapy with thiopentone 0.5 Gm., atropine $\frac{1}{150}$ grain and d-tubocurarine, 30 mg. After shock therapy, the patients were decurarized with neostigmine and then given 50 mg. of NP 13. In all cases, thiopentone anesthesia was rapidly terminated without fasciculations or convulsions. (2) Six patients were anesthetized with thiopentone 0.5 Gm. Following the surgical procedure, the anesthesia was promptly ended by the administration of 50 mg. NP 13. (3) Ten surgical patients received thiopentone 0.5 Gm. and cyclopropane. After short operations the patients recovered quickly after 50 mg. NP 13. In longer operations, the longer time for recovery was attributed to the duration of cyclopropane anesthesia. In one patient with shock, the intravenous injection of 50 mg. of NP 13 had no observable effect, possibly because of the depressant effect of the cyclopropane. The author concludes that NP 13 is a barbiturate antagonist of real clinical worth.

DAVID M. KYDD, M.D.

Vol. 1, February 12, 1955.

*Brown, J. B.: Urinary Excretion of Oestrogens During the Menstrual Cycle, p. 320.

*Morris, Norman, Osborn, S. B., and Wright, H. Payling: Effective Circulation of the Uterine Wall in Late Pregnancy, p. 323.

Morris, J. N., and Heady, J. A.: Social and Biological Factors in Infant Mortality. I. Objects and Methods, p. 343.

Brown: Urinary Excretion of Oestrogens During the Menstrual Cycle, p. 320.

Using a new, accurate, and apparently specific chemical method, the author has determined the excretion of estriol, estrone, and estradiol-17 β during ten normal menstrual

*Titles preceded by an asterisk are abstracted below.

cycles in eight normal women. He confirms previous work and comments that the day-to-day variation in estrogen excretion seems to be more important than the amounts excreted at any one time. Random estimates will have little significance compared with serial determinations.

DAVID M. KYDD, M.D.

Morris, Osborn, and Wright: Effective Circulation of the Uterine Wall in Late Pregnancy: Measured With Na^{24}Cl , p. 323.

The rate at which an injected substance is removed from the injection site depends upon many factors, but over-all it is an index to the effectiveness of local circulation. On this premise, the writers conclude from their experiments that the effective circulation of the uterine wall is significantly decreased in twin pregnancy, diminished by about half in mild pre-eclampsia and by three-fourths in severe pre-eclampsia.

They injected transperitoneally 5 to 10 microcuries of Na^{24} , in 0.3 to 0.4 ml. of isotonic saline, into the uterine wall and measured the rate of disappearance of radioactivity by placing a Geiger-Müller counter over the injection site. In 20 normal women, 34 to 40 weeks pregnant, the mean time to disappearance of half the original activity was 4.1 minutes, with a standard error of 0.354. In 10 patients with mild pre-eclampsia the mean time was 7.7 ± 0.523 minutes. In 8 cases of severe pre-eclampsia the mean was 15.3 ± 2.854 minutes and in 10 twin pregnancies, 6.6 ± 1.054 minutes. Repeated measurements were made in 9 cases, with good checks; the greatest discrepancy in a pair of tests was 0.7 minute.

LEON C. CHESLEY, Ph.D.

Vol. 1, February 19, 1955.

Heady, J. A., Daly, C., and Morris, J. N.: Social and Biological Factors in Infant Mortality. II. Variation of Mortality With Mother's Age and Parity, p. 395.

Vol. 1, February 26, 1955.

Nordin, B. E. C., and Roper, A.: Post-Pregnancy Osteoporosis. A Syndrome? p. 431.

Daly, C., Heady, J. A., and Morris, J. N.: Social and Biological Factors in Infant Mortality. III. The Effect of Mother's Age and Parity on Social-Class Differences in Infant Mortality, p. 445.

Vol. 1, March 5, 1955.

Scrimgeour, J. W. F., and Carrick, J. E.: Fatal Air-Embolism Associated With Ruptured Uterus, p. 485.

Heady, J. A., Stevens, C. F., Daly, C., and Morris, J. N.: Social and Biological Factors in Infant Mortality. IV. The Independent Effects of Social Class, Region, the Mother's Age and Her Parity, p. 499.

Vol. 1, March 10, 1955.

Gunther, Mavis: Instinct and the Nursing Couple, p. 575.

*Forfar, J. O., Maccabe, A. F., Balf, C. L., Wright, H. A., and Gould, J. C.: Staphylococcal Infection in the Newborn. Treated With Erythromycin, p. 584.

Forfar, Maccabe, Balf, Wright, and Gould: Staphylococcal Infection in the Newborn. Treated With Erythromycin, p. 584.

In one hospital 14 per cent of the infants developed infection (conjunctivitis 64 per cent, skin pustules 14 per cent, infection of umbilical stump 9 per cent, local cellulitis 6 per cent, other infections 7 per cent). In a second hospital 13 per cent of the infants became infected (conjunctivitis 61 per cent, skin pustules 24 per cent, infection of cord stump 4 per cent, cellulitis 11 per cent). These infections were caused by the following organisms in the two hospitals, respectively: coagulase-positive staphylococcus 74 per cent and 70 per cent, coagulase-negative staphylococcus 18 per cent and 25 per cent, some

other organism 8 per cent and 5 per cent. In one hospital infants with infection were treated with erythromycin and in the second hospital with erythromycin and streptomycin. The trial continued for nine months and the average duration of treatment was 3.5 and 4.5 days, respectively. There were no failures in the treatment of skin infections, but 8 per cent of the instances of conjunctivitis did not respond and streptomycin did not increase the effectiveness. No strain of *Staphylococcus pyogenes* developed resistance to erythromycin during the test but the proportion of streptomycin-resistant organisms increased. Erythromycin did not interfere with the normal growth of *E. coli* in the intestine. By studying the phage type and antibiotic resistance pattern of the organisms isolated, it is believed that there was a free interchange of staphylococci between staff and infants and between infants and that cross infection was common.

DAVID M. KYDD, M.D.

The Medical Journal of Australia

Vol. 1, No. 4, January 22, 1955.

Lewis, R. J. R.: The Use of the Fern Test for Infertility, p. 105.

Vol. 1, No. 6, February 5, 1955.

*Cobley, J. F. C. C., and Lancaster, H. O.: Carbohydrate Tolerance in Pregnancy, p. 171.

Cobley and Lancaster: Carbohydrate Tolerance in Pregnancy, p. 171.

This study was conducted to supplement the relatively incomplete literature on carbohydrate metabolism during pregnancy. One hundred and fifty-eight women were investigated by glucose tolerance tests performed at monthly intervals throughout their gestations. Fifty grams of oral glucose were administered after the fasting blood sugar levels were determined and then blood glucose analyses were performed at half-hour intervals for three hours.

The ages of the women involved are noted. Histories and physical examinations were part of the initial visit. A summarizing table presents the mean readings of the blood glucose according to the months of pregnancy.

There was no significant variation in the blood sugar curves as the patients neared term. The typical levels were in the following ranges: fasting 85 to 89 mg. per cent, $\frac{1}{2}$ hour 123 to 131 mg. per cent, 1 hour 126 to 133 mg. per cent, $1\frac{1}{2}$ hours 115 to 128 mg. per cent, 2 hours 101 to 114 mg. per cent, $2\frac{1}{2}$ hours 90 to 96 mg. per cent, and 3 hours 81 to 85 mg. per cent. The majority of the highest readings were found in the half-hour and one-hour determinations.

From this publication it may be concluded that pregnancy per se produces little change in the carbohydrate metabolism. Fasting blood sugar levels are within the normal range. There may be some delay in the sugar curve returning to normal values in some pregnant women.

This investigation seems to have been well conducted. Therefore, this report may serve as a base line for those interested in the study of pancreatic functions in the gravid female.

ARTHUR PERELL, M.D.

Vol. 1, No. 8, February 19, 1955.

Kelsall, G. A., and Vos, G. H.: The Foetal and Neonatal Wastage Due to Sensitization by the Rh Factor, p. 261.

Southern Medical Journal

Vol. 48, No. 1, January, 1955.

Hoge, Randolph H.: Arteriovenous Fistula of the Uterus, p. 18.

*Adams, John Quiney, and Packer, Henry: Granuloma Inguinale of the Cervix, p. 27.

Adams and Packer: Granuloma Inguinale of the Cervix, p. 27.

The clinical characteristics of granuloma inguinale are discussed in detail. Methods of clinical and laboratory diagnosis are described. Carcinoma of the cervix is the most important differential diagnosis, since it is suspected in most instances until pathologic diagnosis fails to reveal malignancy. Rapid spread throughout the pelvis may occur during pregnancy because of the increased vascularity and lymphatic supply of the pelvic organs. At delivery deep cervical laceration may occur in the friable and infected cervix with fatal hemorrhage. Streptomycin, oxytetracycline, chlortetracycline, chloramphenicol, and erythromycin have been shown to be specific for the treatment of this disease. Penicillin is ineffective against the Donovan body which is the etiological agent. Patients should receive between 20 and 40 Gm. of any one of these antibiotics over a period of 10 to 20 days in order to obtain the optimum result. Four cases are reported which were treated with carbomycin (Magnamycin). From 10 to 15 Gm. of carbomycin was administered with therapeutic failure in 2 instances. Oxytetracycline was then administered with complete healing. The authors conclude that carbomycin has no therapeutic advantage over other antibiotics from the standpoint of the duration of treatment or the dosage of drug required.

STEWART A. FISH, M.D.

Vol. 48, No. 2, February, 1955.

*Black, William T., Jr.: Presacral Neurectomy: Report of 70 Cases, p. 120.

Ausherman, H. M.: Anesthesia for the Elderly Patient, p. 130.

*Sherman, Alfred I., and Ruch, Robert M.: Eclampsia: A Review of 173 Cases Studied at St. Louis Maternity Hospital, p. 142.

Black: Presacral Neurectomy, p. 120.

The author discusses the differential diagnosis of dysmenorrhea and emphasizes the necessity for careful selection of patients. The author's criteria are: (1) primary dysmenorrhea which has been unsuccessfully treated for prolonged periods with conservative methods including estrogen, thermal therapy, and antispasmodics; (2) secondary dysmenorrhea (e.g. endometriosis) in patients too young for radical operation; (3) dysmenorrhea in patients of any menstrual age whose uterus and at least a part of one ovary are salvageable. In this last group presacral neurectomy is used in conjunction with definitive conservative surgery for endometriosis or pelvic inflammatory disease. Individuals with dysmenorrhea of ovarian origin are not candidates for presacral neurectomy.

A technique for presacral neurectomy is described after a brief anatomic consideration of the presacral nerve. The author achieved about 90 per cent lasting benefit in the 70 cases reported. Over half the patients with primary dysmenorrhea noted relief of dyspareunia and improved libido. Of ten patients who subsequently became pregnant, six suffered little or no pain during labor while two were not benefited. Of the patients with primary dysmenorrhea, 67 per cent noted complete relief from pain and 18 per cent were improved. In those patients with acquired dysmenorrhea, 47 per cent were completely relieved and 7 per cent were improved. The author notes in conclusion that the majority of patients only partially relieved by presacral neurectomy felt that the operation was well worth while.

STEWART A. FISH, M.D.

Sherman and Ruch: Eclampsia: A Review of 173 Cases Studied at St. Louis Maternity Hospital, p. 142.

During the period from 1927 to 1954, 165 cases fulfilling the criteria for the diagnosis of eclampsia were seen at the St. Louis Maternity Hospital. Five cases of eclampsia superimposed on existing hypertension or chronic glomerulonephritis are excluded from the series. There were 3 instances of "eclampsia without convulsion." The incidence, mortality, treatment, and prognosis of these cases are tabulated and discussed. The authors conclude that the most important lesson gained from this study is the advantage of con-

servative therapy. The majority of patients who did poorly or died were the ones who were treated radically. The authors note that 19 per cent of the eclamptic patients who were normotensive before pregnancy developed persistent hypertension following their episodes of eclampsia. Normal subsequent pregnancy was seen in 80 per cent of the individuals who could be followed.

STEWART A. FISH, M.D.

The Western Journal of Surgery, Obstetrics and Gynecology

Vol. 63, January, 1955.

- *Moore, J. G.: Growth Characteristics in Tissue Culture of Controversial Lesions of the Uterine Cervix, p. 1.
- *Banks, A. Lawrence, and Rutherford, Robert N.: Vaginal Hysterectomy. Individual Variation in Technic and End-Results, p. 23.
- *Krahulik, Emil J.: The Emancipation of the Accoucheur, p. 37.
- Rutherford, Robert N.: The Metabolic Concept of Gynecologic Care, p. 48.

Moore: Growth Characteristics in Tissue Culture of Controversial Lesions of the Uterine Cervix, p. 1.

The author, from prior studies, had observed that the behavior in tissue culture of normal cervical epithelium and cervical epidermoid carcinoma varied. The normal cervical epithelium was difficult to grow whereas malignant epidermoid epithelium grew extensively with relative consistency. So with this observation of differential growth potential he decided to apply tissue culture methods to selected controversial cervical lesions which histologically occupied an intermediate position.

Over a two-year period (1952-1954) cervical tissue was obtained for biopsy and tissue culture studies from 27 patients with cervical carcinoma, 8 nonpregnant patients with normal cervixes, 8 pregnant patients with normal cervixes, and 8 cases wherein the tissue study was controversial. Later 12 additional cases, questionable as to whether the cervical lesion was in situ or else early invasive in character, were added. In three-fourths of this group there were no presenting symptoms.

In the tissue culture specimens from the 27 patients with unquestionably malignant lesions he observed a good growth response in 23 patients. He found that among the controversial lesions those diagnosed as in situ carcinoma or minimally invasive carcinoma grew with equal facility to the tissue from the frankly invasive carcinoma.

In his conclusion the author discusses the obvious drawbacks. Tissue culture is tedious, expensive, and requires considerable patience. Further, a negative response does not necessarily mean that a malignant process is absent. However, a rapid, and extensive growth response in culture of tissue from the adult cervix is highly suggestive of the presence of a malignancy.

CLAIR E. FOLSOME, M.D.

Banks and Rutherford: Vaginal Hysterectomy. Individual Variation in Technic and End-Results, p. 23.

The authors review 120 vaginal hysterectomies from their private practices over a four-year period. The majority of these operations were accompanied by various vaginal reparative procedures on the posterior or anterior vaginal walls.

The writers stress their strong preference for vaginal hysterectomy, reasoning that this procedure offers the most rapid and uncomplicated recovery. They indicate the usual contraindications to this operation. They stress strongly the preoperative and postoperative care of each patient upon an individualized basis. They approach this procedure on the assumption that the need for repair of the entire pelvic floor exists but can be edited to suit the individual case. The authors then succinctly delineate their method of vaginal hysterectomy with 6 figures.

Banks and Rutherford obtained uniformly good postoperative results which they attribute to the careful selection of cases plus individualization of each case. They had no recurrence of vaginal prolapse. They attribute this to special attention in the plication of the cardinal ligaments to the pubocervical fascia of the other side, thus giving the vagina increased depth and ensuring the integrity of the central point of support of the vault.

CLAIR E. FOLSOME, M.D.

Krahulik: Emancipation of the Accoucheur, p. 37.

The author in a presidential address before the Pacific Coast Obstetrical and Gynecological Society reviews the considerable progress that has been made in obstetrical practice in the past 40 years. He attributes much of this progress to broader training and experience plus a gentler attitude toward labor and toward the resolution of the various obstetrical complications that have depressed the maternal and infant mortality rates. While the section rate has increased, cesarean section has become safe and deservedly replaces many mutilating procedures practiced in the past.

The author concludes that public opinion held the obstetrician responsible for the unhappy episodes in his practice. This load has been decreased considerably though he still shoulders a few items for which he is not responsible.

CLAIR E. FOLSOME, M.D.

Die Medizinische

No. 2, January 8, 1955.

Lillge, M.: The Treatment of Erosion of the Cervix and Vaginitis With Aristogyn, p. 87.

No. 6, February 5, 1955.

Englhardt-Goelkel, A., and Prosielgel, R.: Biochemical Basis and Modern Clinical Uses of ACTH and Cortisone, p. 216.

No. 7, February 12, 1955.

Heller, L.: The Treatment of Complaints of Pregnancy, p. 241.

Zetzmann, M.: A Contribution to the Question of Induced Abortion, p. 243.

Schmidt, H.: Contribution to the Clinical Aspects of Toxoplasmosis, p. 247.

Reissner, A.: Some Observations on Female Sexual Behavior, p. 259.

No. 8, February 19, 1955.

*Bayer, W.: Nutrition of the Expectant Mother—Prophylaxis for the Child, p. 273.

Bayer: Nutrition of the Expectant Mother—Prophylaxis for the Child, p. 273.

A considerable body of evidence from animal experiments and clinical experience is presented, indicating that maternal malnutrition can lead to malformations and neonatal disease. For instance, in the years following the war, when there was a particular lack of food in Germany, the incidence of anencephaly was more than twenty-five times that of the prewar figure. In rats, litters without eyes can be produced by maternal diets deficient in vitamin A during the first trimester. As another example, children of mothers with diets deficient in vitamin D almost invariably develop rickets at the age of about 2 months.

The well-known effects on the fetus of maternal diabetes mellitus and toxemia of pregnancy are also mentioned. The author lays great stress on the importance of proper nutrition and well-regulated metabolism in the expectant mother as a factor in reducing perinatal mortality and neonatal disease.

WALTER F. TAUBER, M.D.

No. 10, March 5, 1955.

Gropper, H.: Data on the New Treponema Antigen and the Serology of Syphilis, p. 352.

No. 12, March 19, 1955.

*Reich, E.: The Treatment of Pre-eclampsia with Pendiamid, a Ganglion-Blocking Agent, p. 414.

Reich: Treatment of Pre-eclampsia With Pendiamid, a Ganglion-Blocking Agent, p. 414.

The author reports on 35 cases of pre-eclampsia treated with a ganglion-blocking agent (Pendiamid), compared to a control series of 37 cases. Both groups had the usual supportive therapy, i.e., salt-free diet, sedation, and dehydration. In no patient in the Pendiamid series did the disease progress to the state requiring immediate termination of pregnancy, while 12 patients in the control series had to be subjected to cesarean section. This is very important since prematurity is a large factor in perinatal mortality in toxemia of pregnancy.

Lowering of the blood pressure was accompanied by lowering of spinal fluid pressure, disappearance of visual disturbances, edema, and cylindruria. Severe cases (blood pressure 175/115) were treated by intravenous or intramuscular injections, while less severe cases (blood pressure 150/100) showed good results with oral administration.

Incidentally, it was found that ganglion blockade shortens the first stage of labor.

WALTER F. TAUBER, M.D.

No. 13, March 26, 1955.

Engelmann, W.: Therapy With Radium Derivatives, p. 449.

No. 14, April 2, 1955.

Smirk, F. H.: The Treatment of Hypertension With Hexamethylammonium Salts and Pentamethylene 1,5-bis-N-(N-methyl-pyrrolidine) Bitartrate, p. 485.

No. 16, April 16, 1955.

Brazel, E.: On the Treatment of Vaginal Bleeding in Gynecological Practice, p. 608.

No. 17, April 23, 1955.

Bautze, H. J.: Anesthesia for Breech Delivery, p. 648.

Hotz, L.: The Treatment of Anuria in Transfusion Reactions, p. 653.

The Journal of Pediatrics

Vol. 46, March, 1955.

Nisenson, Aaron, Isaacson, Alvin, and Grant, Sidney: Masklike Facies With Associated Congenital Anomalies (Möbius Syndrome), p. 255.

Arnold, Gayle G.: Perforation of the Stomach in the Neonatal Period, p. 276.

Colt, James, Hart, Wayne, and Mayer, John H.: A Rare Type Esophageal Anomaly and Its Treatment, p. 317.

Vol. 46, April, 1955.

Reimann, D. L., Clemmens, R. L., and Pillsbury, W. A.: Congenital Acute Leukemia, p. 415.

Vol. 46, May, 1955.

*Arnold, Douglas P., Witebsky, Ernest, Selkirk, George H., and Alford, Kenneth M.: Clinical and Serological Experiences in Treating Hemolytic Disease of the Newborn, p. 520.

Arnold et al.: Clinical and Serological Experiences in Treating Hemolytic Disease of the Newborn, p. 520.

The authors present their results on the treatment of 243 babies born alive with hemolytic disease. Since 1949, 217 infants have received 240 replacement transfusions with a neonatal loss rate of only 2.5 per cent.

They also describe a modification of the Witebsky test for diagnosis of hemolytic disease due to Rh or ABO incompatibility.

The use of the saphenous vein is emphasized and sound reasons presented for its preferential use over the umbilical vein.

The entire report is clear, nicely illustrated with case reports, up to date, and generally informative.

SCHUYLER G. KOHL, M.D.

Vol. 46, June, 1955.

Briggs, J. Nixon: A Clinical Trial of Aleveire in Pulmonary Distress of the Newborn Infant, p. 621.

Journal of Obstetrics and Gynaecology (Northern India)

Vol. 16, February, 1955.

Bhonsale, I. N.: Two Unusual Cases of Ectopic Pregnancy, p. 29.

Vohra, S.: Observations on the Average Weight of Normal Infants Born in the Memorial Hospital Ludhiana During the Years 1951-54, p. 34.

Vol. 16, March, 1955.

Sagar, V.: Psychiatric Aspects of Certain Gynaecological Problems, p. 47.

The Journal of the American Geriatrics Society

Vol. 3, February, 1955.

Tyler, F. H., Eik-Nes, K., Sanberg, A. A., Florentin, A. A., and Samuels, L. T.: Adrenocortical Capacity and the Metabolism of Cortisol in Elderly Patients, p. 79.

Elman, R.: Surgical Experience in the Aged as an Aid to Surgery in the Young, p. 85.

Hunnicut, A. J.: Physiologic Reserves in the Aged: Application to Operability, p. 93.

Vol. 3, April, 1955.

*Morris, John McLean: Gynecologic Carcinoma in the Older Patient, p. 259.

Morris: Gynecologic Carcinoma in the Older Patient, p. 259.

The author points out that the age specific incidence of gynecologic cancer, except of vulval origin, falls after the seventh decade in contradistinction to the sharp rise in other forms of cancer. The relationship of the age specific incidence to etiology is speculative—perhaps some endocrine factor may be involved.

The results achieved in 53 patients 65 years or over with gynecologic cancer are reviewed at the end of two years. Forty per cent were either dead or living with residual disease. This figure is nearly twice that in a similar group of patients under 60 years of age. Seventy-five per cent of the deaths or recurrences were in patients whose disease was so extensive when first seen as to make the cases hopeless from the onset. This may well indicate neglect of either patient or physician origin.

In the treatment of elderly patients with cervical cancer, Dr. Morris recommends radiation therapy because of the lower incidence of urinary complications, and the lower mortality and morbidity rates. He found the cytologic studies of radiation sensitivity and response to be a valuable criterion in 48 cases. In 17 with good response, there were 3 recurrences; in 23 with poor response, there were 11 recurrences. In the patients with endometrial carcinoma, combined radiation therapy and surgery are advocated. Except in poor-risk patients, a pelvic lymph node dissection was performed. In approximately 25 per cent of the cases there were positive nodes.

In discussing the requirements of therapy, the author states that to obtain maximal benefits from radiation, the program must include flexibility and individualization. In general, radiation doses are 20 per cent lower in elderly patients. Accurate measurements

with scintillation counters should be obtained during radium therapy. The nature of the tumor and its anatomic extent will influence the therapeutic management of an individual case. Centralization of treatment in institutions of experience appears to offer the patients a better chance. The author concludes that it is important to avoid injury or death in those who can be cured, and to avoid making life more miserable for those who cannot.

JOHN G. MASTERSON, M.D.

American Journal of the Medical Sciences

Vol. 229, June, 1955.

Heindorn, G. H., and Schemm, F. R.: The Clinical Use of Corticotropin (ACTH) and Adrenal Corticosteroids in the Therapy of Intractable Edema, p. 621.

Parrish, A. E., Rubinstein, N. H., and Howe, J. S.: Correlation Between Renal Function and Histology, p. 632.

*Lange, R. D., and Hagen, P. S.: Hemoglobin C Disease in Identical Twins, p. 655.

Lange and Hagen: Hemoglobin C Disease in Identical Twins, p. 655.

A pair of 25-year-old, Negro, male, identical twins were found at a routine physical examination to have enlarged spleens and mild anemia. Reticulocytosis and numerous target cells were seen in the blood smear. The red cells did not sickle. There was an increased fecal excretion of urobilinogen. Autotransfused tagged cells had a markedly shortened survival time. Despite the increased hemolysis, the disease apparently is benign. Electrophoretic studies of their hemoglobin showed hemoglobin C as the only form of hemoglobin, indicating homozygosity for the condition. Another brother has the sickle-cell trait, one sister is homozygous and another heterozygous for hemoglobin C.

LEON C. CHESLEY, PH.D.

The Irish Journal of Medical Science

Sixth Series, No. 351, March, 1955.

*Moore, H. C., Lillie, E. H., and Gatenby, P. B. B.: The Response of Megaloblastic Anaemia of Pregnancy to Vitamin B₁₂, p. 106.

*Browne, Alan D. H., and Mannion, Patrick L.: The Application of Chlorpromazine to Obstetrics, With a Study of Its Effects During Labour, p. 117.

*O'Keeffe, W. P., Shanahan, J., and Quane, M. B.: Chlorpromazine in Eclampsia, p. 124.

Moore, Lillie, and Gatenby: Response of Megaloblastic Anaemia of Pregnancy to Vitamin B₁₂, p. 106.

Seventeen cases of megaloblastic anemia of pregnancy at the Rotunda Hospital were treated with vitamin B₁₂. Six patients also received iron therapy. Fecal fat analysis was performed during a four-day period with the patients on a standard diet containing 70 grams of fat and 70 grams of protein daily.

Thirteen patients had a reticulocyte response to therapy. The four cases which did not respond to vitamin B₁₂ therapy responded favorably to subsequent folic acid therapy.

The authors conclude that "there are two groups of megaloblastic anemia of pregnancy depending on the response to vitamin B₁₂, and not all cases can be regarded as folic acid deficient anemias."

SCHUYLER G. KOHL, M.D.

Browne and Mannion: Application of Chlorpromazine to Obstetrics, With a Study of Its Effects During Labour, p. 117.

Sixty-eight patients were given one or more doses of 25 mg. of Largactil orally with and without 100 mg. of pethidine (Demerol) intramuscularly. They classified their patients for analysis in the following groups:

1. Primiparas who received Largactil and had a normal delivery—18 patients.
2. Multiparas who received Largactil and had a normal delivery—34 patients.

3. "Patients of assorted parity" who received Largactil and had an operative delivery other than cesarean section—16 patients.

The patients in Group 1 all became drowsy after administration of the initial dose. Their babies were drowsy and lethargic for several hours after birth. It is thought that the drug aids relaxation between contractions and potentiates the action of Demerol when given with it. It was successful 68 per cent of the time, but subjectively much less so. The duration of labor was thought to be decreased. If given too early in labor, it appears to diminish uterine activity.

In Group 2 there were 31 successful cases, and there was no decrease in the duration of labor.

In Group 3 the results were less desirable. It seemed to have slowed labor to such an extent as to require operative delivery. It was also observed here that when the drug was given "too soon before delivery, its effect was poor, and the baby seemed more drowsy than the average."

While "the labour ward was never quieter," one gets the impression that the drug may be of little value. The impression is that this report from the Rotunda is not as complete as is desired to reach a decision.

SCHUYLER G. KOHL, M.D.

O'Keeffe, Shanahan, and Quane: Chlorpromazine in Eclampsia, p. 124.

This report on the use of Thorazine in an eclamptic patient discloses that it controlled convulsions when other forms of therapy failed. When the patient was released from Thorazine therapy, the convulsions recurred.

The authors found eight cases of eclampsia previously treated with this drug and reported from the European continent. In none of the cases, however, was the drug used alone. It has always been employed along with other agents: magnesium sulfate, barbiturates, or paraldehyde.

SCHUYLER G. KOHL, M.D.

Sixth Series, No. 353, May, 1955.

Feeney, J. K.: Accidental Haemorrhage, p. 195.

Shea, S. M.: Fibrinolysis in the Puerperium, p. 233.

The Journal of Clinical Endocrinology and Metabolism

Vol. 15, June, 1955.

- *Hodges, R. E., Evans, T. C., Bradbury, J. T., and Keettel, W. C.: Accumulation of I^{131} by Human Fetal Thyroids, p. 661.

Hodges, et al.: Accumulation of I^{131} by Human Fetal Thyroids, p. 661.

The authors gave patients who required therapeutic abortions 500 microcuries of I^{131} approximately twenty-four hours before surgical intervention. Immediately after the operation the fetuses were photographed and the thyroid glands removed in a block of tissue including the trachea. The radioactivity of the thyroid was measured. Routine sections and radioautograph slides were made.

The results indicate that the human fetal thyroid has the ability to accumulate demonstrable amounts of I^{131} by the twelfth week of gestation. It is questionable whether or not the accumulation of iodine is enough to preclude I^{131} therapy of thyrotoxicosis during pregnancy.

Three cases are cited where pregnant women were given radioactive iodine and the infants were normal. Possibly the amount of iodine absorbed by the fetal thyroid was insufficient to cause trouble or the increased thyroxine present in thyrotoxicosis depressed the ability of the fetal thyroid to absorb much iodine.

J. EDWARD HALL, M.D.

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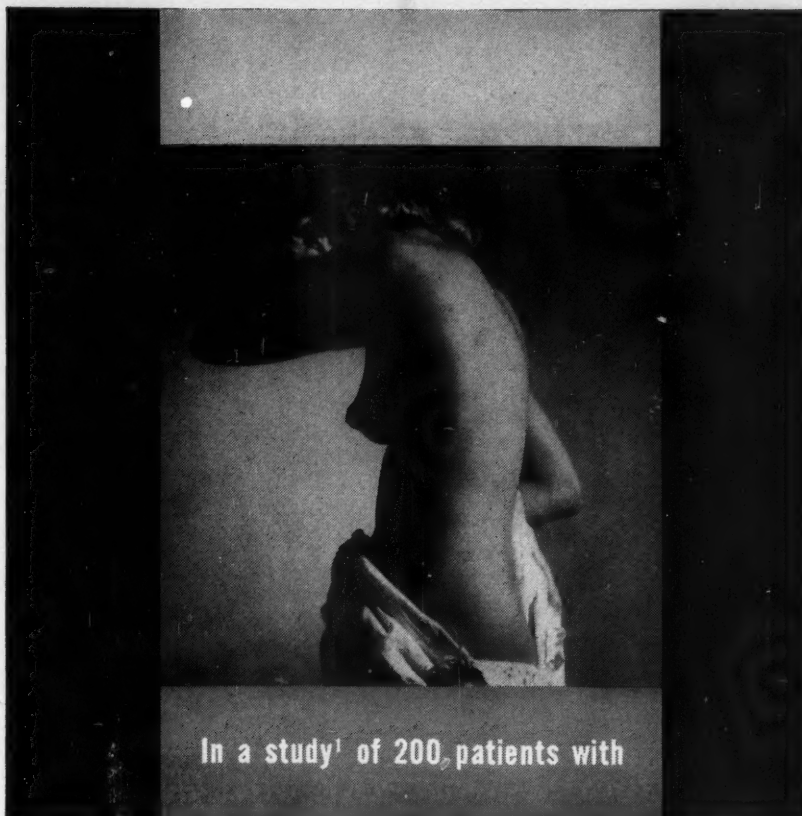
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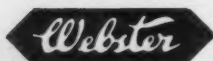
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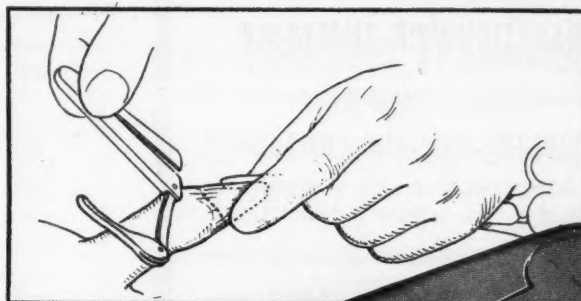
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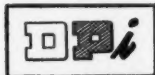
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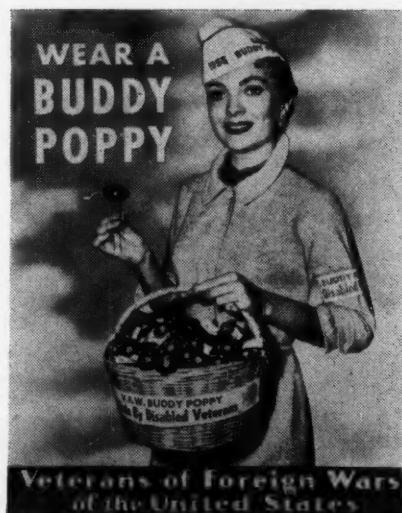
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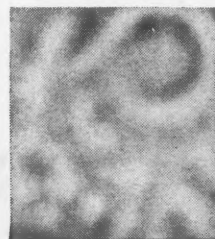
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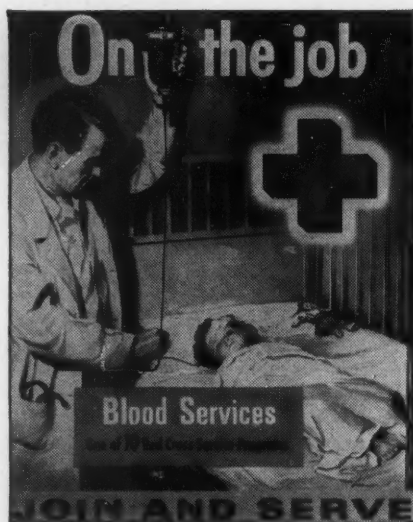
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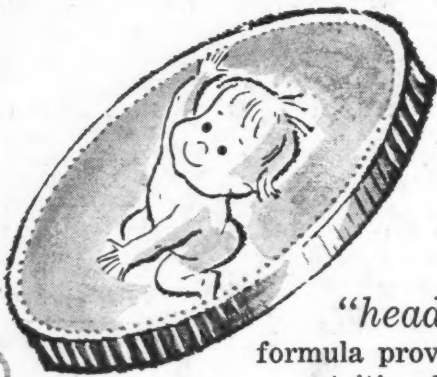
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either way
you win
with **Bremil**[®]



"heads"... because a BREMIL formula provides a *complete* nutritional intake that consistently promotes infant growth and development at or above accepted standards¹; made with grade A milk.



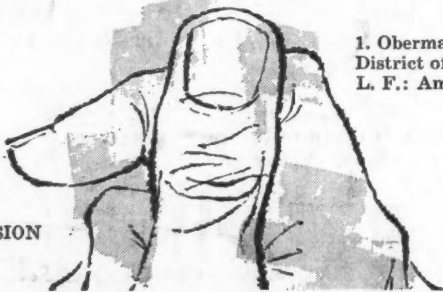
"tails"... because the easily digested, efficiently utilized protein content of BREMIL (approximating that of breast milk) virtually eliminates excoriations due to ammonia dermatitis¹, and does not impose an excessive solute load on the immature kidney²

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One level measure to 2 fluidounces of hot water. Mixes like a liquid. Costs no more than ordinary formulas requiring vitamin and carbohydrate supplementation. In 1-lb. tins at all drug outlets.

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PRESCRIPTION PRODUCTS DIVISION
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1. Oberman, J. W., and Burke, F. G.: M. Ann. District of Columbia 23:483, 1954. 2. Hill, L. F.: Am. J. Clin. Nutrition 3:75, 1955.